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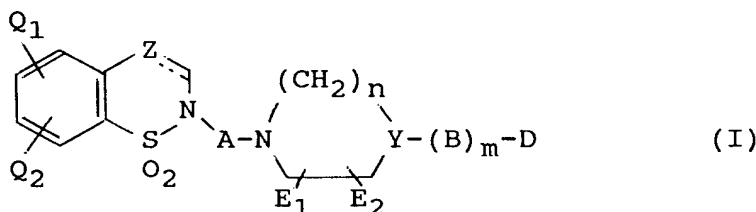
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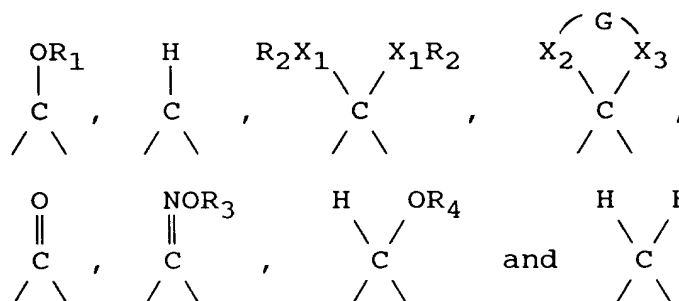
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(54) **Substituted benzothiazine derivative**

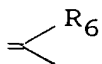
(57) Disclosed are substituted benzothiazine derivatives represented by the following formula (I):



wherein the dashed line indicates the presence or absence of a bond; Z represents one of the following groups:



in which R_1 and R_2 individually represent alkyl, aralkyl or the like, R_3 represents H, alkyl or the like, R_4 represents H, aralkyl or the like, X_1 , X_2 and X_3 individually represent O or S, and G represents substituted or unsubstituted ethylene, trimethylene or the like; Q_1 represents H, OH, halogen, alkoxy or the like; Q_2 is similar to Q_1 except for the exclusion of H; A represents alkylene, alkenylene or the like; Y represents CH, C= or N; when Y is CH, m stands for 0 or 1, n stands for 1 or 2, B represents O, S, carbonyl or the like, when Y is C=, m stands for 1, n stands for 1 or 2, B represents:



in which the double bond is linked to Y, R₆ represents substituted or unsubstituted aryl or the like; when Y is N, m stands for 0 or 1, n stands for 2 or 3, B represents carbonyl, sulfonyl or the like, E₁ and E₂ individually represent H or lower alkyl; and D represents an aromatic hydrocarbon group or an aromatic heterocyclic group; and salts thereof.

The substituted benzothiazine derivatives (I) and their salts according to the present invention have strong serotonin-2 blocking action, have excellent selectivity to this action against α_1 blocking action and have high safety. Accordingly, the present invention has made it possible to provide pharmaceuticals making use of antagonistic action against serotonin-2 receptors, for example, therapeutics for various circulatory diseases such as ischemic heart diseases, cerebrovascular disturbances and peripheral circulatory disturbances.

Description

This invention relates to novel substituted benzothiazine derivatives. More specifically, this invention is concerned with substituted benzothiazine derivatives and salts thereof, said derivatives and salts being useful for the prevention or treatment of ischemic heart diseases such as angina pectoris, arrhythmia, myocardial infarction, congestive heart failure and post-PTCA restenosis, cerebrovascular disturbances such as cerebral infarction and cerebral sequelae after subarachnoid hemorrhage, and/or peripheral circulatory disturbances such as arteriosclerosis obliterans, Raynaud disease, Buerger disease and thrombophlebitis; their preparation process; and pharmaceuticals comprising them as effective ingredients.

Serotonin is a compound contained abundantly in platelets, which are a blood component, and in a central nervous system, it acts as a neurotransmitter. In platelets, it is released upon stimulation by thromboxane A_2 , ADP, collagen or the like and synergistically acts on various platelet aggregation factors or vasoconstrictors through activation of serotonin-2 receptors in the platelets and vascular smooth muscle cells, thereby inducing strong platelet aggregation and vasoconstriction [P.M. Vanhoutte, "Journal of Cardiovascular Pharmacology", Vol. 17 (Supple. 5), S6-S12 (1991)].

Serotonin is also known to potentiate proliferation of vascular smooth muscle cells [S. Araki et al., "Atherosclerosis", Vol. 83, p29-p34(1990)]. It has been considered that, particularly when endothelial cells are injured as in arteriosclerosis or myocardial infarction, the vasoconstricting action and thrombus forming action of serotonin are exasperated, thereby reducing or even stopping blood supply to myocardial, cerebral and peripheral organs [P. Golino et al., "The New England Journal of Medicine", Vol. 324, No. 10, p641-p648(1991), Y. Takiguchi et al., "Thrombosis and Haemostasis", Vol. 68(4), p460-p463(1992), A.S. Weyrich et al., "American Journal of Physiology", Vol. 263, H349-H358(1992)].

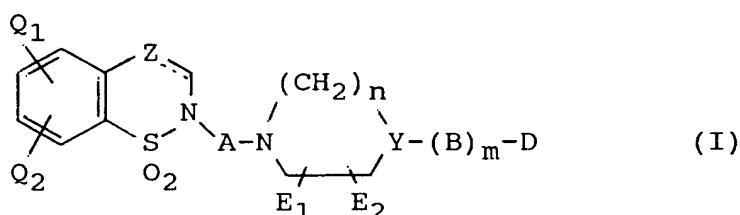
Being attracted by such actions of serotonin or serotonin-2 receptors, various attempts are now under way to use a serotonin-2 receptor antagonist as a pharmaceutical for ischemic diseases of the heart, the brain and peripheral tissues.

Ketanserin which has therapeutically been used as a hypotensive drug is known as a compound having antagonistic action against a serotonin-2 receptor. Ketanserin has strong antagonistic action against a sympathetic nerve α_1 receptor and also against histamine-1 and dopamine receptors in addition to antagonistic action against serotonin-2 receptors so that there is the potential problem of developing excessive hypotensive action, neuroleptic action or the like when used for the treatment of ischemic heart disease or peripheral circulatory disturbance. Ketanserin is therefore not preferred.

In addition, several compounds led by sarpogrelate are known to have serotonin-2 receptor antagonistic action. They, however, are accompanied with problems in the potency, the selectivity against other receptors, toxicity, side effects or the like. Thus, there remains still much room for improvements.

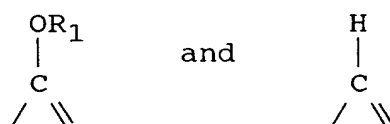
In view of the foregoing circumstances, it has been found that specific substituted benzothiazine derivatives have strong serotonin-2 receptor antagonistic action, is excellent in the selectivity of a serotonin-2 receptor in the antagonistic action against various receptors, particularly in the selectivity to a serotonin-2 receptor in the antagonistic action against α_1 receptor, and have low toxicity, leading to the completion of the present invention.

The present invention has been completed based on the above described findings and a first object of the present invention is to provide a benzothiazine derivative represented by the following formula (I):

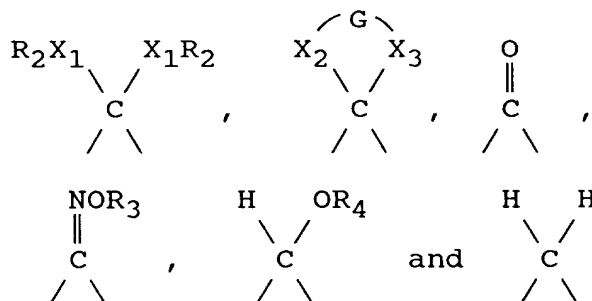


wherein the dashed line indicates the presence or absence of a bond and when the bond indicated by the dashed line is present,

Z represents one of the following groups:



in which R_1 represents a substituted or unsubstituted alkyl group or a substituted or unsubstituted aralkyl group but, when the bond indicated by the dashed line is absent, Z represents one of the following groups:



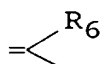
wherein R_2 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, R_3 represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, R_4 represents a hydrogen atom, a substituted or unsubstituted alkyl group or a substituted or unsubstituted aralkyl group, X_1 , X_2 and X_3 each independently represents an oxygen atom or a sulfur atom, G represents an ethylene group with one or more of the hydrogen atoms thereof optionally substituted by a like number of halogen atoms and/or alkyl, aryl, aralkyl and/or alkylidene groups or a trimethylene group with one or more of the hydrogen atoms thereof optionally substituted by a like number of halogen atoms and/or alkyl, aryl, aralkyl and/or alkylidene groups,

Q_1 represents a hydrogen atom, a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aralkyloxy group,

Q_2 represents a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aralkyloxy group,

A represents a substituted or unsubstituted alkylene group, a substituted or unsubstituted alkenylene group or a substituted or unsubstituted alkynylene group,

Y represents CH, C= or a nitrogen atom; and, when Y represents CH, m stands for 0 or 1, n stands for 1 or 2, and B represents an oxygen atom, a sulfur atom, a carbonyl group, a sulfinyl group, a sulfonyl group, an alkylene group, an alkenylene group, a substituted or unsubstituted hydroxymethylene group, a group -CHR₅- in which R_5 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted cyclic or acyclic acetal group, when Y represents C=, m stands for 1, n stands for 1 or 2, and B represents:



in which the double bond is linked to Y, R_6 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, but, when Y represents a nitrogen atom, m stands for 0 or 1, n stands for 2 or 3, and B represents a carbonyl group, a sulfonyl group, an alkylene group, an alkenylene group or a group -CHR₇- in which R_7 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group,

E_1 and E_2 each independently represents a hydrogen atom or a lower alkyl group, and

D represents a substituted or unsubstituted aromatic hydrocarbon group or a substituted or unsubstituted aromatic heterocyclic group; or a salt thereof.

Another object of the present invention is to provide a preparation process of the substituted benzothiazine derivative (I) or its salt.

A further object of the present invention is to provide a pharmaceutical such as a therapeutic for circulatory diseases or the like, said pharmaceutical containing the substituted benzothiazine derivative (I) or its pharmacologically-acceptable salt thereof as an effective ingredient.

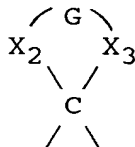
The substituted benzothiazine derivatives (I) and their salts according to the present invention have strong serot-

onin-2 blocking action, have excellent selectivity to this action against α_1 blocking action and have high safety.

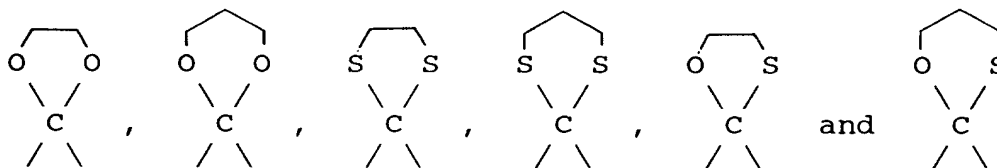
In the substituted benzothiazine derivatives (I) of the present invention, preferred examples of group R_1 include branched or linear C_{1-4} alkyl groups such as methyl and ethyl and C_{7-22} aralkyl groups such as benzyl and phenethyl, each of which may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C_{1-4} alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C_{1-4} alkoxy groups such as methoxy and ethoxy.

Preferred examples of group R_2 include branched or linear C_{1-4} alkyl groups such as methyl and ethyl, C_{6-14} aryl groups such as phenyl and naphthyl and C_{7-22} aralkyl groups such as benzyl and phenethyl, each of which may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C_{1-4} alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C_{1-4} alkoxy groups such as methoxy and ethoxy. In this case, preferred examples of group R_2X_1 include methoxy, methylthio, ethoxy and ethylthio groups.

Preferred examples of the following group:



includes groups represented by the following formulas:

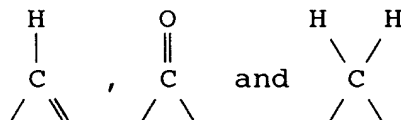


in which one or more of the hydrogen atoms may be substituted by a corresponding number of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C_{1-4} alkyl groups such as methyl and ethyl; aryl groups, preferably C_{6-14} aryl groups such as phenyl and naphthyl; aralkyl groups, preferably C_{7-22} aralkyl groups such as benzyl and phenethyl; and/or alkylidene groups, preferably C_{1-4} alkylidene groups such as methylenidene and ethylenidene.

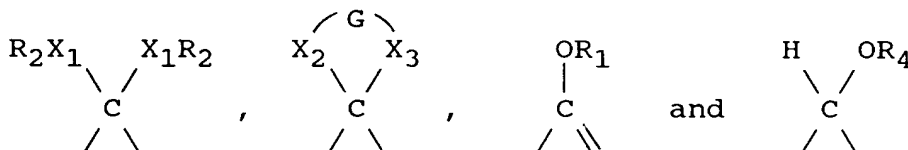
Preferred examples of group R_3 of group NOR_3 include a hydrogen atom, branched or linear C_{1-4} alkyl groups such as methyl and ethyl, C_{6-14} aryl groups such as phenyl and naphthyl and C_{7-22} aralkyl groups such as benzyl and phenethyl. Each of the exemplified groups may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C_{1-4} alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C_{1-4} alkoxy groups such as methoxy and ethoxy.

Preferred examples of group R_4 include a hydrogen atom, branched or linear C_{1-4} alkyl groups such as methyl and ethyl and C_{7-22} aralkyl groups such as benzyl and phenethyl. Each of the exemplified groups may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C_{1-4} alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C_{1-4} alkoxy groups such as methoxy and ethoxy.

Preferred examples of group Z include the following group:



Specifically preferred examples of the group Z include the following groups:



wherein G, R₁, R₂, R₄, X₁, X₂ and X₃ have the same meanings as defined above.

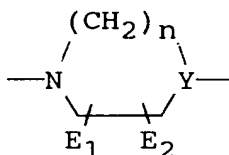
Preferred examples of Q₁ include a hydrogen atom; a hydroxyl group; halogen atoms such as fluorine, chlorine and bromine; branched or linear C₁₋₄ alkyl groups such as methyl and ethyl; branched or linear C₁₋₄ alkoxy groups such as methoxy and ethoxy; C₇₋₂₂ aralkyl groups such as benzyl and phenethyl; and C₇₋₂₂ aralkyloxy groups such as benzyloxy and phenethyloxy. Each of the exemplified groups may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy. Of these Q₁, particularly preferred include a hydrogen atom, a methoxy group, a chlorine atom and the like.

Preferred examples of Q₂ include a hydroxyl group; halogen atoms such as fluorine, chlorine and bromine; branched or linear C₁₋₄ alkyl groups such as methyl and ethyl; branched or linear C₁₋₄ alkoxy groups such as methoxy and ethoxy; C₇₋₂₂ aralkyl groups such as benzyl and phenethyl; and C₇₋₂₂ aralkyloxy groups such as benzyloxy and phenethyloxy. Each of the exemplified groups may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy. Of these Q₂, particularly preferred include a methoxy group, a chlorine atom and the like.

Further, preferred examples of substituting positions and combinations of Q₁ and Q₂ include combinations of a hydrogen atom as Q₁ and 5-hydroxy, 5-chloro, 5-bromo, 5-methyl, 5-ethyl, 5-n-propyl, 5-isopropyl, 5-n-butyl, 5-s-butyl, 5-methoxy, 5-ethoxy, 5-n-propoxy, 5-isopropoxy, 5-benzyloxy, 6-hydroxy, 6-fluoro, 6-chloro, 6-methyl, 6-ethyl, 6-n-propyl, 6-methoxy, 6-ethoxy, 6-n-propoxy, 6-benzyloxy, 7-hydroxy, 7-fluoro, 7-chloro, 7-methyl, 7-ethyl, 7-n-propyl, 7-methoxy, 7-ethoxy, 7-n-propoxy, 7-benzyloxy, 8-hydroxy, 8-fluoro, 8-chloro, 8-methyl, 8-ethyl, 8-n-propyl, 8-methoxy, 8-ethoxy, 8-n-propoxy and 8-benzyloxy as Q₂; and also combinations of 5,7-dihydroxy, 6,7-dichloro, 5,8-dimethyl, 6,8-dimethyl, 5,6-dimethoxy, 5,7-dimethoxy, 5,8-dimethoxy and 6,7-dimethoxy as Q₁ and Q₂.

Preferred examples of group A include branched or linear C₂₋₁₀ alkylene groups such as ethylene, trimethylene, tetramethylene, pentamethylene and octamethylene, branched or linear C₄₋₁₀ alkenylene groups such as 2-butenylene and 3-pentenylene groups; and branched or linear C₄₋₁₀ alkynylene groups such as 2-butyne and 3-pentyne groups. Each of the exemplified group may be substituted by one or more of halogen atoms such as fluorine, chlorine and bromine. Among them, ethylene, trimethylene and tetramethylene groups are particularly preferred.

The group, which is represented by the following formula:



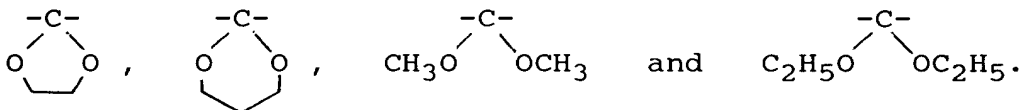
wherein E₁, E₂, Y and n have the same meanings as defined above, is a heterocyclic group led by a pyrrolidine, piperidine, piperazine or homopiperazine group, in which two or less hydrogen atoms on the ring may be substituted by lower alkyl groups, preferably C₁₋₄ alkyl groups such as methyl or ethyl.

When the group of the above formula is a heterocyclic group derived from pyrrolidine or piperidine, preferably a piperidine group, m stands for 0 or 1 with the proviso that m is 1 when Y represents C=, and B represents an oxygen atom, a sulfur atom, a carbonyl group, a sulfinyl group, a sulfonyl group, an alkylene group (preferably a C₁₋₄ alkylene group and most preferably a methylene group), an alkenylene group (preferably C₂₋₅ alkenylene group and most preferably a 2-propenylene group), a substituted or unsubstituted hydroxymethylene group, a group -CHR₅- (in which R₅ preferably represents a C₁₋₄ alkyl group such as methyl and ethyl; a C₆₋₁₄ aryl group such as phenyl or naphthyl; or a C₇₋₂₂ aralkyl group such as benzyl or phenethyl, which may be substituted), the following group:



wherein the double bond is linked to Y, and R₆ represents an alkyl group, preferably a C₁₋₄ alkyl group such as methyl and ethyl; an aryl group, preferably C₆₋₁₄ aryl group such as phenyl and naphthyl; and an aralkyl group, preferably a C₇₋₂₂ aralkyl group such as benzyl and phenethyl, which may be substituted), cyclic acetal or acyclic acetal group in which one or more of hydrogen atoms may be substituted.

Exemplary cyclic or acyclic acetal groups include the following groups:



Preferred examples of a substituent group for the hydroxymethylene group represented by B include alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl and aryl groups, preferably C₆₋₁₄ aryl groups such as phenyl and naphthyl, all substituted to the carbon atom of the methylene group. Further, they can be substituted by one or more of hydroxyl groups, halogen atoms such as fluorine, chlorine and bromine and/or alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy.

Particularly preferred examples of the substituted or unsubstituted hydroxymethylene group include an unsubstituted hydroxymethylene group and hydroxymethylene groups substituted by a phenyl, fluorophenyl or hydroxyphenyl group.

Further, examples of one or more substituent groups for R₅ include one or more halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; and alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy.

Illustrative of one or more substituent groups for R₆ include one or more halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy; and hydroxyl groups. Examples of one or more substituent groups for the cyclic or acyclic acetal include halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; aryl groups, preferably C₆₋₁₄ aryl groups such as phenyl and naphthyl; aralkyl groups, preferably C₇₋₂₂ aralkyl groups such as benzyl and phenethyl; and alkylidene groups, preferably C₁₋₄ alkylidene groups such as methylidene and ethylidene.

Among these illustrative examples of the group represented by B, especially preferred is a carbonyl group.

When the heterocyclic group is a group derived from piperazine or homopiperazine, preferably a piperazine group, m stands for 0 or 1 (preferably 0) and B represents a carbonyl group, a sulfonyl group, an alkylene group (preferably a C₁₋₄ alkylene group, particularly a methylene group), an alkenylene group (preferably C₃₋₆ alkenylene group, particularly 2-propenylene group) or a group -CHR₇- (in which R₇ represents an alkyl group, preferably a C₁₋₄ alkyl group such as methyl and ethyl; an aryl group, preferably C₆₋₁₄ aryl group such as phenyl and naphthyl; and an aralkyl group, preferably a C₇₋₂₂ aralkyl group such as benzyl and phenethyl).

R₇ may in turn be substituted by one or more halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; and/or alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy.

Of the above-described examples of group B, preferred is a substituted or unsubstituted phenylmethylene group.

Preferred examples of group D include aromatic hydrocarbon groups, preferably C₆₋₂₈ aromatic hydrocarbon groups such as a phenyl group with one or more of its hydrogen atoms having been optionally substituted and a naphthyl group with one or more of its hydrogen atoms having been optionally substituted. Other preferred examples of group D include aromatic heterocyclic groups, preferably monocyclic or bicyclic ones with three or fewer oxygen, sulfur and/or nitrogen atoms - such as pyridyl, pyrimidinyl, benzisothiazolyl, benzisoxazolyl and indolyl groups with one or more hydrogen atoms thereof having been optionally substituted.

Examples of substituent groups for the aromatic hydrocarbon groups and aromatic heterocyclic groups include halogen atoms such as fluorine, chlorine and bromine; alkyl groups, preferably C₁₋₄ alkyl groups such as methyl and ethyl; alkoxy groups, preferably C₁₋₄ alkoxy groups such as methoxy and ethoxy; aryl groups, preferably C₆₋₁₄ aryl groups such as phenyl and naphthyl; aralkyl groups, preferably C₇₋₂₂ aralkyl groups such as benzyl and phenethyl; aralkyloxy

groups, preferably C_{7-22} aralkyloxy groups such as benzyloxy; cyano group; nitro group; carboxyl group; alkoxycarbonyl group (the number of carbons in the alcohol moiety preferably ranges from 1 to 6); lower alkylsulfonylamino groups (the number of carbon atoms in the alkyl moiety preferably ranges from 1 to 4); a carbamoyl group; and a hydroxyl group.

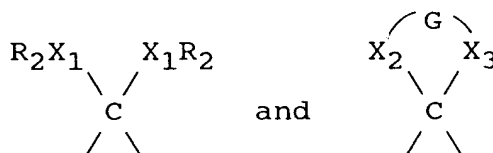
Of these illustrative groups represented by D, preferred are phenyl groups unsubstituted or substituted by one or more of halogen atoms, alkoxy groups and hydroxyl groups, benzisothiazolyl groups unsubstituted or substituted by one or more halogen atoms, benzisoxazolyl groups unsubstituted or substituted by one or more halogen atoms, and indazolyl groups unsubstituted or substituted by one or more halogen atoms. Particularly preferred are phenyl groups unsubstituted or substituted by one or more of fluorine atoms, methoxy groups and hydroxyl groups.

Many of the compounds (I) according to the present invention have isomers. It is to be noted that these isomers and mixtures thereof are all embraced by the present invention.

Various processes can be employed for the preparation of the substituted benzothiazine derivatives (I) according to the present invention. It is however preferred to prepare the benzothiazine derivatives, for example, by any one of the following processes.

Process 1:

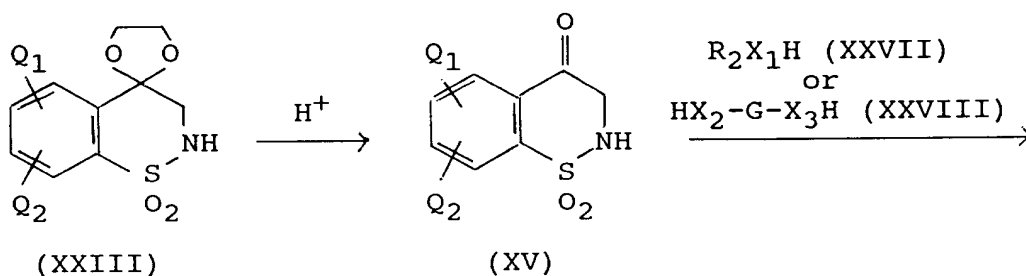
Among the substituted benzothiazine derivatives (I), each of compounds (Ib) in which Z is represented by one of the following formulas:

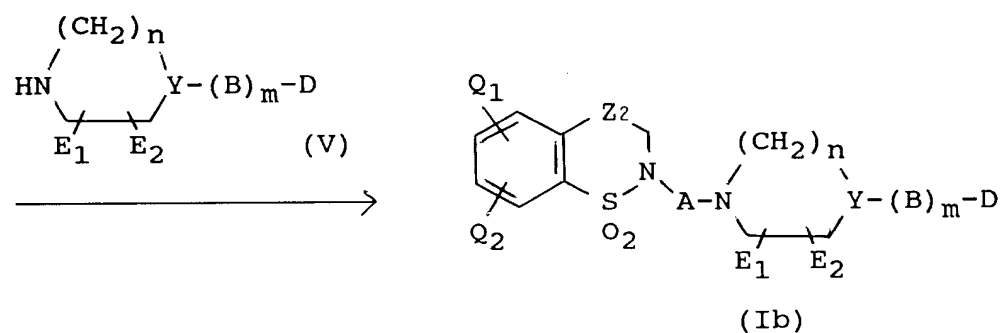
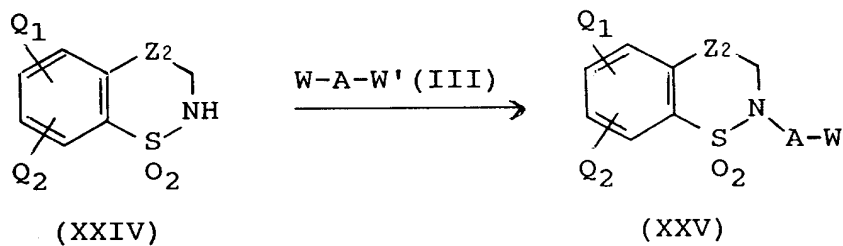


can be synthesized in accordance with any of the processes shown by the following schemes.

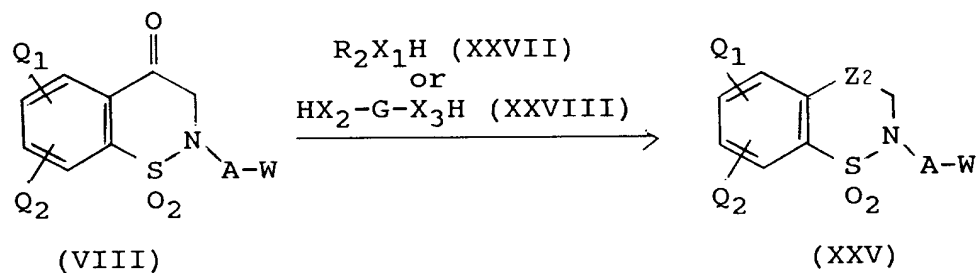
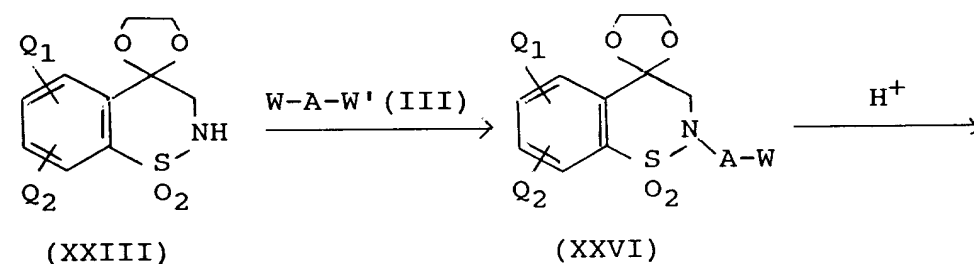
(a) Following the below-described reaction scheme, a compound represented by the formula (XXIII) is treated with an acid into a compound represented by the formula (XV), followed by the reaction with the a compound represented by the formula (XXVII) or the formula (XXVIII) into a compound represented by the formula (XXIV). The compound (XXIV) is reacted with a compound represented by the formula (III) so that the former compound is converted to a compound represented by the formula (XXV). The compound (XXV) is reacted further with a nitrogen-containing compound represented by formula (V) or a salt thereof, whereby a compound (Ib) is obtained.

As an alternative process for obtaining the compound (XXV) from the compound (XXIII), it is possible to adopt a process in which, after the compound (III) is reacted to the compound (XXIII), the reaction product is subjected to deacetalization, followed by the reaction with the compound (XXVII) or the compound (XXVIII).

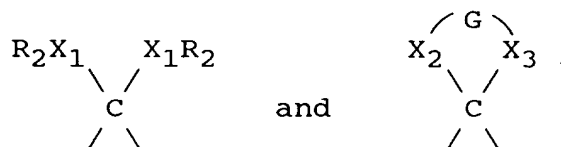




(Alternative Process)



wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above; Z₂ represents one of the following groups:



in which G, R₂, X₁, X₂ and X₃ have the same meanings as defined above; and W and W' may be the same or dif-

ferent and individually represents a substituent easily replaceable with an amino group.

In the above reactions, the conversion from the compound (XXIII) to the compound (XV) or that from the compound (XXVI) to the compound (VIII) in the alternative process can be effected choosing a suitable process described T.W. Green in "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc. or the like. As a typical example, a process in which an acid such as hydrochloric acid or acetic acid is caused to act on the compound (XXIII) or the compound (XXVI) can be mentioned.

Further, the conversion from the compound (XV) to the compound (XXIV) or that from the compound (VIII) to the compound (XXV) in the alternative process can be effected choosing an adequate process described by T.W. Green in "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc. or the like. As a typical example, a process in which ethylene glycol, ethanedithiol, ethanethiol or the like is caused to act on the compound (XV) in the presence of an acid can be mentioned.

In the above reactions, the conversion from the compound (XXIV) to the compound (XXV) or that from the compound (XXIII) to the compound (XXVI) in the alternative process can be effected by causing the compound (III) to act on the compound (XXIV) or the compound (XXIII) after treating the compound (XXIV) or the compound (XXIII) with an inorganic base or an organic base, or by causing the compound (III) to act on the compound (XXIV) or the compound (XXIII) in the presence of such a base.

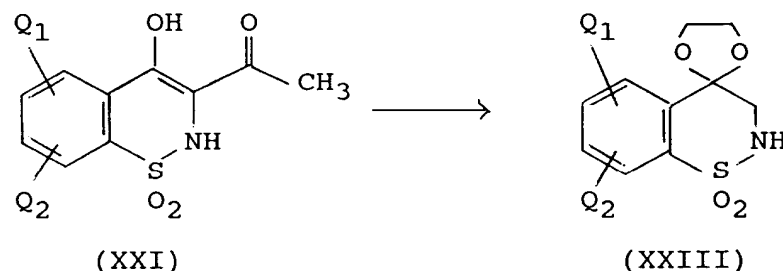
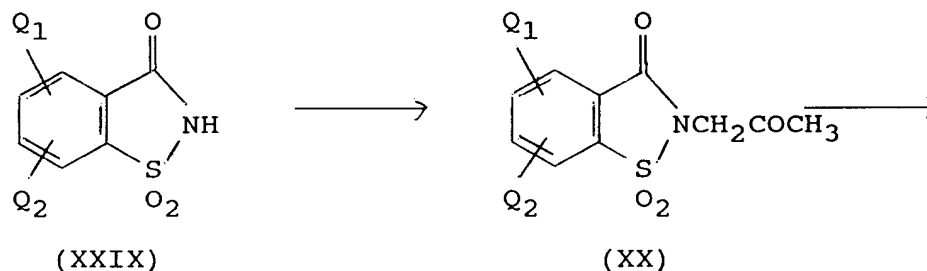
Examples of group W or W' of the compound (III), which is an eliminative substituent and is easily replaceable with an amino group, include halogen atoms such as chlorine and bromine, alkylsulfonyloxy groups such as methanesulfonyloxy and arylsulfonyloxy groups such as p-toluenesulfonyloxy.

On the other hand, exemplary inorganic or organic bases include sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, triethylamine and Potassium t-butoxide. Further, illustrative solvents useful for the above reaction include tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide, acetonitrile, N-methylpyrrolidone, acetone, 2-butanone and toluene. The reaction is conducted at -78°C to reflux temperature.

To prepare the compound (Ib) by reacting the thus-obtained compound (XXV) with the nitrogen-containing compound (V), it is only necessary to react the nitrogen-containing compound (V) or an organic acid salt or inorganic acid salt thereof with the compound (XXV), optionally together with an organic base such as triethylamine, pyridine, collidine, 1,8-diazabicyclo[5.4.0]undec-7-en (DBU) or potassium t-butoxide or an inorganic base such as potassium carbonate, sodium carbonate, sodium hydrogencarbonate, sodium hydroxide or sodium hydride, optionally after adding an alkali iodide such as potassium iodide or sodium iodide, at 0°C to 150°C in the solvent exemplified above or a solvent such as methanol, ethanol, propanol or butanol.

Examples of the nitrogen-containing compound (V) include 1-phenylpiperazine, 1-(2-fluorophenyl)piperazine, 1-(3-fluorophenyl)piperazine, 1-(4-fluorophenyl)piperazine, 1-(4-hydroxyphenyl)piperazine, 1-(2-chlorophenyl)piperazine, 1-(3-chlorophenyl)piperazine, 1-(4-chlorophenyl)piperazine, 1-(2-methoxyphenyl)piperazine, 1-(3-methoxyphenyl)piperazine, 1-(4-methoxyphenyl)piperazine, 1-(4-methanesulfonamidophenyl)piperazine, 1-(4-cyanophenyl)piperazine, 1-(4-carbamoylphenyl)piperazine, 1-(4-methoxycarbonylphenyl)piperazine, 1-(2-pyridyl)piperazine, 1-(2-pyrimidinyl)piperazine, 1-benzylpiperazine, 1-diphenylmethylpiperazine, 1-cinnamylpiperazine, 1-benzoylpiperazine, 1-(4-benzyloxybenzoyl)piperazine, 1-(4-hydroxybenzoyl)piperazine, 1-(2-furoyl)piperazine, 1-(1,2-benzisoxazol-3-yl)piperazine, 1-(1,2-benzisothiazol-3-yl)piperazine, 4-phenylpiperidine, 4-benzylpiperidine, α,α -bis(4-fluorophenyl)-4-piperidinemethanol, 4-(4-fluorobenzoyl)piperidine, 4-benzoylpiperidine, 4-(4-methoxybenzoyl)piperidine, 4-(4-chlorobenzoyl)piperidine, 3-(4-fluorobenzoyl)piperidine, 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, 4-(6-fluoro-1,2-benzisothiazol-3-yl)piperidine, 4-(6-fluoro-1H-indazol-3-yl)piperidine, 3-benzoylpyrrolidine, 3-(4-fluorobenzoyl)pyrrolidine, 4-(4-fluorophenoxy)piperidine, 4-[(4-fluorophenyl)thio]piperidine, 4-[(4-fluorophenyl)sulfinyl]piperidine, 4-[(4-fluorophenyl)sulfonyl]piperidine, 4-[bis(4-fluorophenyl)methylene]piperidine and 4-(4-fluorobenzoyl)piperidine ethylene acetal. They are all either known compounds or compounds which can be readily prepared by a known process or a process similar to the known process.

In the above reactions, the compound (XXIII) employed as the starting material can be prepared using as a raw material a saccharin derivative represented by the formula (XXIX) in accordance with the following reaction scheme:



25 wherein Q_1 and Q_2 have the same meanings as defined above.

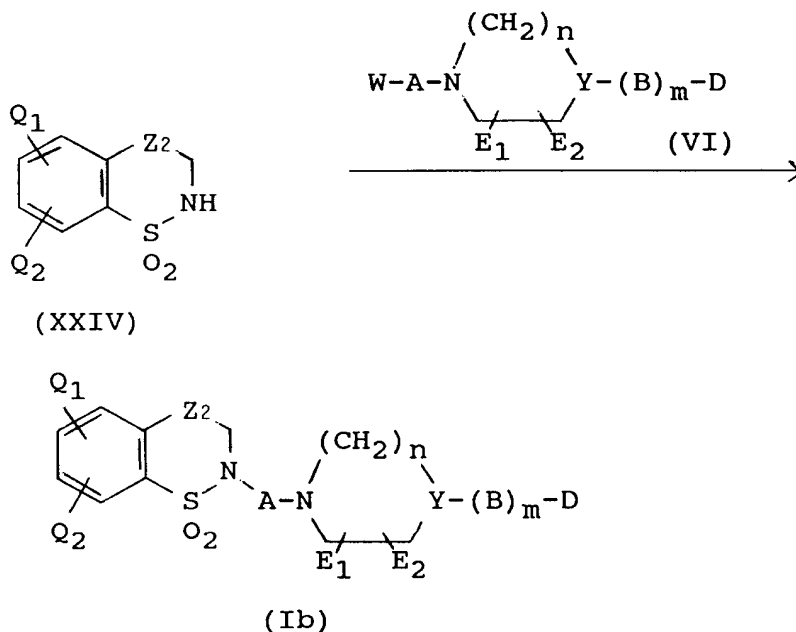
In the above reactions, the conversion from the compound (XXIX) to the compound (XX) can be conducted using the process proposed by E. Eckenroth in Ber., **29**, 329 (1896), and the conversion from the compound (XX) to the compound (XXI) can be conducted using the process proposed by H. Zinnes in J. Org. Chem., **30**, 2241 (1965). Further, the conversion from the compound (XXI) to the conversion (XXIII) can be performed using the process proposed by H. Zinnes in J. Org. Chem., **31**, 162 (1966).

Substituted saccharins (XXIX) usable as starting materials in the above reactions are either known compounds or compounds which can be readily prepared by a known process or a process similar to the known process. For example, preparation processes for saccharins substituted by one or more hydroxyl groups are disclosed in JP-A-56-166181, JP-A-61-215382, etc., while preparation processes for saccharins substituted by one or more halogen atoms such as fluorine, chlorine and bromine atoms were proposed, for example, by W. Davies in J. Chem. Soc., **119**(I), 876 (1921), by F. Becke et al. in Liebigs Ann. Chem., **729**, 146 (1969), by J.G. Lombardino in J. Org., Chem., **36**, 1843 (1971) and by Nitta et al. in Yakugaku Zasshi, **84**, 496 (1964) and are also disclosed in JP-A-52-71464, JP-A-56-166181, JP-A-5-194444, etc.

Further, preparation processes for saccharins substituted by one or more alkyl groups such as methyl groups were proposed by J.G. Lombardino in J. Org. Chem., **36**, 1843 (1971) and are disclosed in JP-A-52-71464, JP-A-61-215382, JP-A-5-194444, etc. and preparation processes for saccharins substituted by one or more alkoxy groups such as methoxy groups were proposed by J.G. Lombardino in J. Org. Chem., **36**, 1843 (1971) and are disclosed in JP-A-52-71464, JP-A-56-166181, JP-A-61-263961, JP-A-5-194444, etc.

Accordingly, substituted saccharins (XXIII) containing desired substituent groups as Q_1 and Q_2 can be obtained by these processes or by processes derived with reference to such processes.

(b) The target compound can be obtained by causing a nitrogen-containing compound represented by the formula (VI) or a salt thereof to act on the compound represented by the formula (XXIV) in accordance with the following reaction scheme:

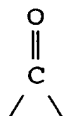


wherein A, B, D, E_1 , E_2 , Q_1 , Q_2 , W, Y, Z_2 , m and n have the same meanings as defined above.

The conversion from the compound (XXIV) to the compound (Ib) can be conducted by causing the compound (VI) to act on the compound (XXIV) after treatment of the latter compound with an inorganic base or an organic base or in the presence of the base. Reaction conditions are similar to those employed in the conversion from the compound (XXIV) to the compound (XXV) in Process 1(a). In this case, it is also possible to add an alkali iodide such as potassium iodide or sodium iodide as needed. Incidentally, the compound (VI) can be synthesized by reacting the compound (V) with the compound (III) in a manner known *per se* in the art.

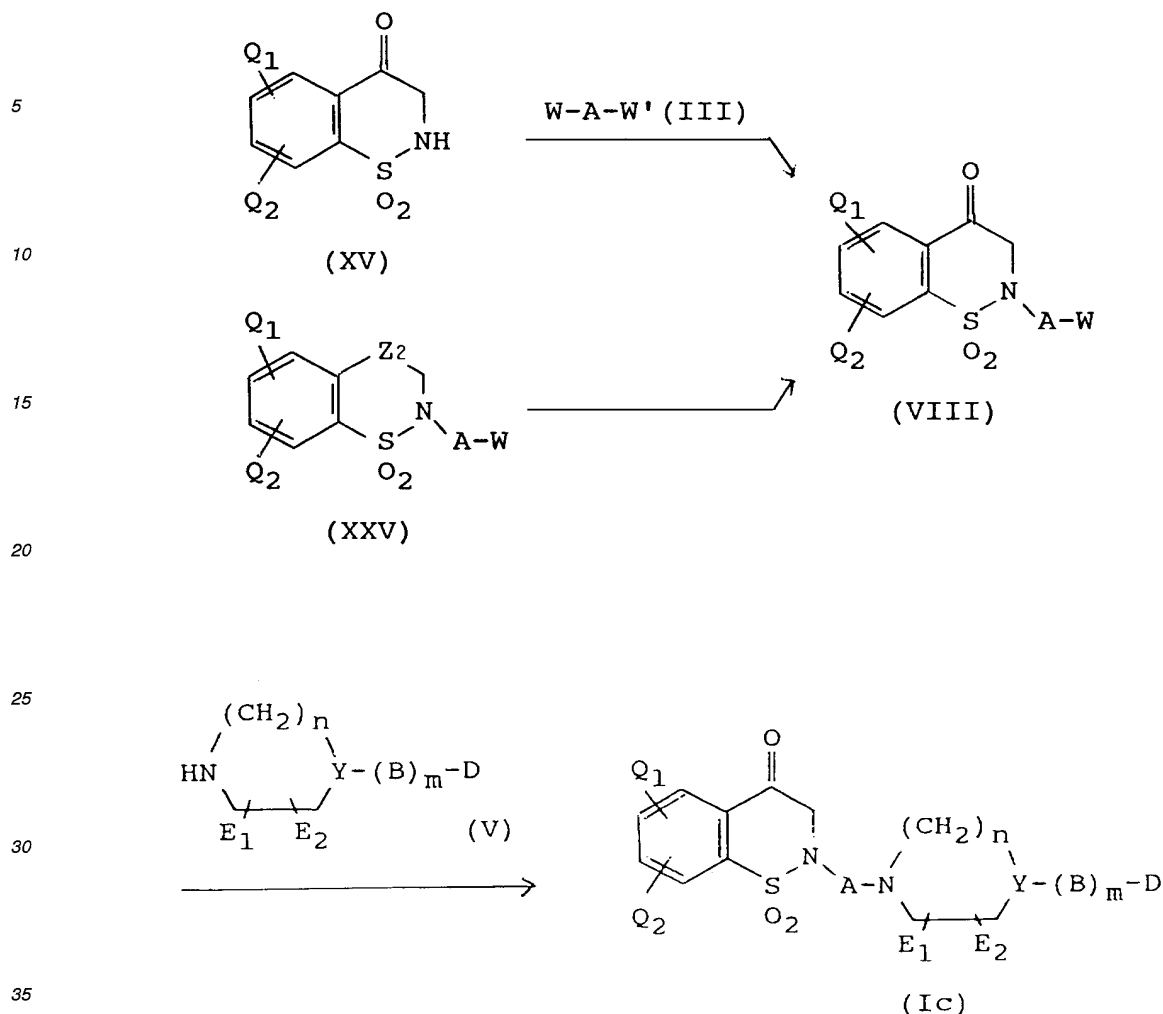
Process 2:

Among the substituted benzothiazine derivatives (I), each of compounds (Ic) in which Z is represented by the following formula:



can be synthesized in any one of the following processes.

(a) The target compound can be obtained, in accordance with the following reaction scheme, by converting a compound (XV) or (XXV) to a compound (VIII) and then reacting the compound (VIII) with a compound represented by the formula (V):

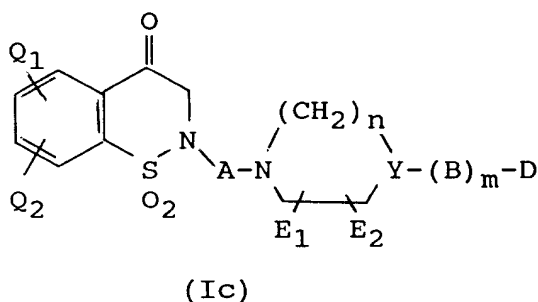
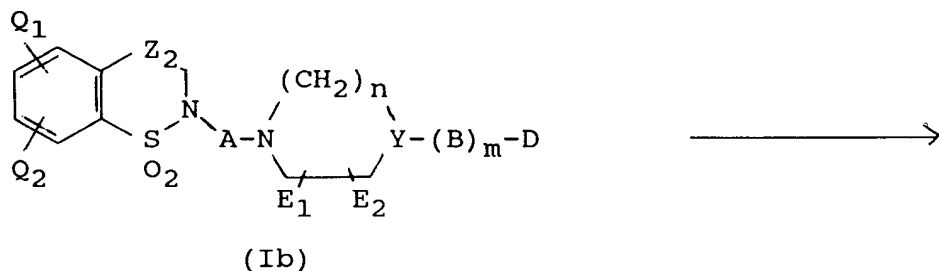


wherein A, B, D, E_1 , E_2 , Q_1 , Q_2 , W, W', Y, Z_2 , m and n have the same meanings as defined above.

The conversion from the compound (XV) to the compound (VIII) can be effected under conditions similar to those employed upon conversion from the compound (XXIV) to the compound (XXV) shown in Process 1(a). Further, the conversion from the compound (XXV) to the compound (VIII) can be effected employing the process described by T.W. Greene in "Protective Groups in Organic Synthesis", John Wiley & Sons, Inc. and the like. For instance, the conversion to the target compound (VIII) can be conducted by acid treatment of the compound (XXV) when in Z_2 , X_1 represents an oxygen atom or X_2 and X_3 both represent an oxygen atom, or by the treatment with mercury (II) chloride when X_1 represents a sulfur atom or X_2 and X_3 both represent a sulfur atom.

The conversion from the compound (VIII) to the compound (Ic) can be effected under conditions similar to those employed upon conversion from the compound (XXV) to the compound (Ib) shown in Process 1(a).

(b) The target compound can be obtained by the conversion of the group Z_2 of the compound (Ib) to a carbonyl group in accordance with the following reaction scheme.

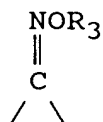


25 wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, Z₂, m and n have the same meanings as defined above.

The conversion from the compound (Ib) to the compound (Ic) can be effected under conditions similar to those employed in the conversion from the compound (XXV) to the compound (VIII) shown in Process 2(a).

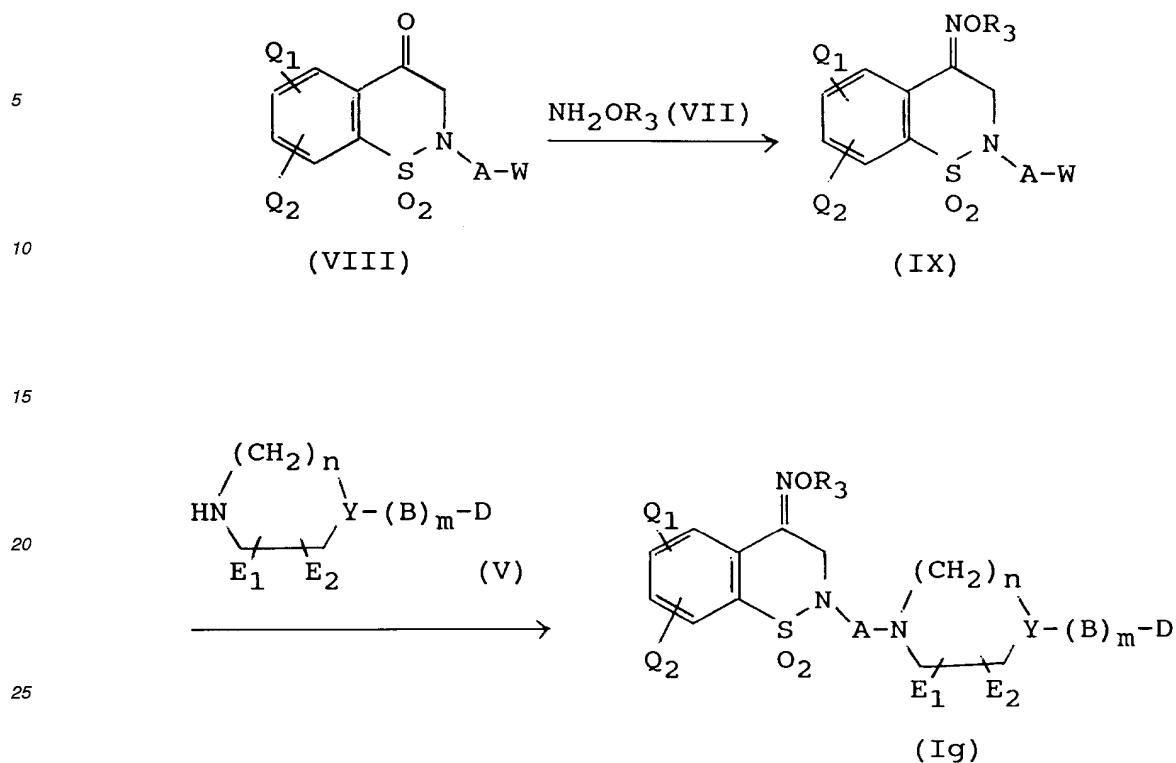
Process 3:

30 Among the substituted benzothiazine derivatives (I), each of the compounds (Ig) and (Ie) in which Z is represented by the following formula:



40 can be synthesized in accordance with any one of the following processes. Selection of process (a) is desired where a nitrogen-containing compound (V) contains a group reactive to a hydroxylamine or a derivative thereof (VII) or a salt of the hydroxylamine or the derivative.

45 (a) Each compound (Ig) can be obtained, in accordance with the following reaction scheme, by causing a hydroxylamine or a derivative thereof represented by the formula (VII) or a salt of the hydroxylamine or the derivative thereof to act on the compound represented by the formula (VIII) and then causing the nitrogen-containing compound (V) to act further.

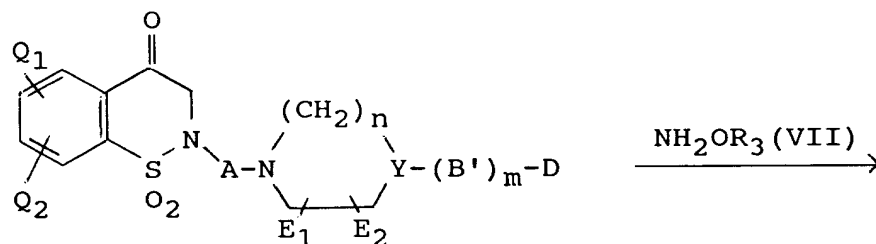


wherein A, B, D, E_1 , E_2 , Q_1 , Q_2 , R_3 , W, Y, m and n have the same meanings as defined above.

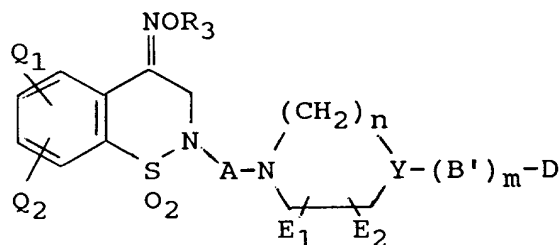
The reaction between the compound (VIII) and the hydroxylamine or its derivative (VII) can be practiced, if necessary, in the presence of an organic base such as pyridine, triethylamine, collidine, DBU or sodium acetate or an inorganic base such as potassium carbonate or sodium hydroxide. The hydroxylamine or its derivative (VII) may also be used in the form of an organic acid salt or an inorganic acid salt.

The reaction is conducted at 0°C to reflux temperature, preferably 0°C to 100°C optionally in a suitable solvent such as methanol, ethanol, propanol, tetrahydrofuran, dimethylformamide or dimethylsulfoxide.

The conversion from the thus-obtained compound (IX) to the compound (Ig) can be effected under conditions similar to those employed in the conversion from the compound (XXV) to the compound (Ib) shown in Process 1(a). (b) Each compound (Ie) can be obtained, in accordance with the following reaction scheme, by causing a hydroxylamine or a derivative thereof (VII) or a salt of the hydroxylamine or the derivative to act on the compound (Id):



(Id)



(Ie)

25

30

wherein, when Y represents CH, B' represents an oxygen atom, a sulfur atom, a sulfinyl group, a sulfonyl group, an alkylene group, an alkenylene group, a substituted or unsubstituted hydroxymethylene group, a group -CHR₅- in which R₅ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted cyclic or acyclic acetal group, when Y represents C=, B' represents the following group:



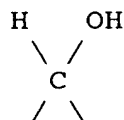
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in which the double bond is linked to Y, R₆ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, but, when Y represents a nitrogen atom, B' represents a carbonyl group, a sulfonyl group, an alkylene group, an alkenylene group or a group -CHR₇- in which R₇ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, and A, D, E₁, E₂, Q₁, Q₂, R₃, Y, m and n have the same meanings as defined above.

The conversion from the compound (Id) to the compound (Ie) can be effected under conditions similar to those employed in the conversion from the compound (VIII) to the compound (IX) shown in Process 3(a).

45 Process 4:

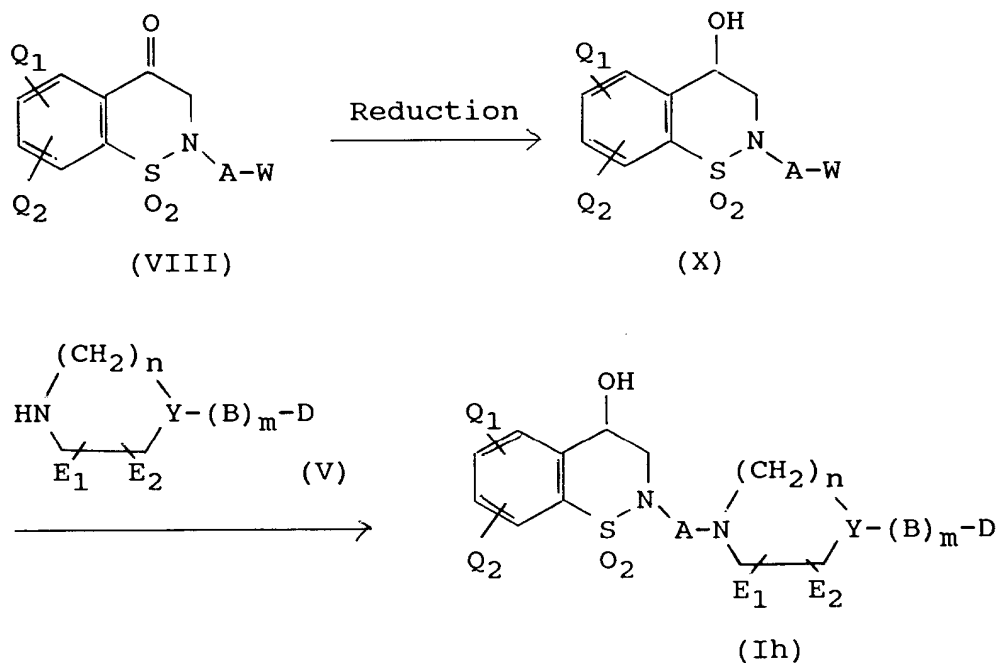
Among the substituted benzothiazine derivatives (I), each of compounds (Ih) and (If) in which Z is represented by the following formula:



can be synthesized by any one of the following processes.

Incidentally, it is desired to select process (a) when there is a group reactive with a reducing agent in a nitrogen-containing compound (V).

(a) Each compound (Ih) can be obtained, in accordance with the following reaction scheme, by reducing the compound represented by the formula (VIII) to obtain the compound (X) and then causing the nitrogen-containing compound (V) to act on the resulting compound.

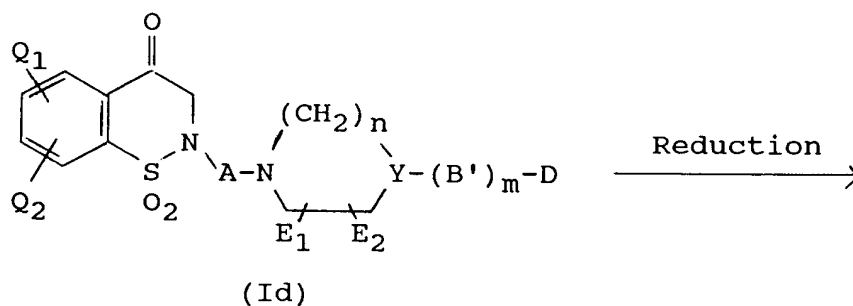


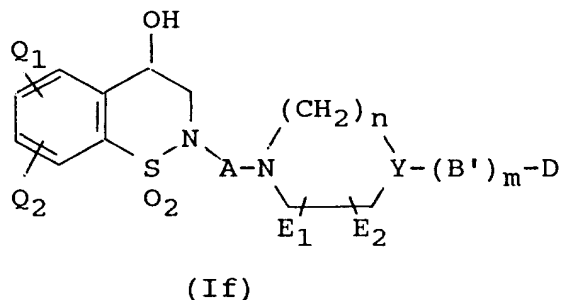
wherein A, B, D, E_1 , E_2 , Q_1 , Q_2 , W, Y, m and n have the same meanings as defined above.

The conversion from the compound (VIII) to the compound (X) can be effected by treating the compound represented by the formula (VIII) with a reducing agent such as sodium borohydride, potassium borohydride or sodium cyanoborohydride in a conventionally-employed solvent at -78°C to reflux temperature, preferably -20°C to room temperature.

Further, the conversion from the compound (X) to the compound (Ih) can be effected under conditions similar to those employed in the conversion from the compound (XXV) to the compound (Ib) shown in Process 1(a).

(b) Each compound (If) can be obtained by reducing the compound (Id) in accordance with the following reaction scheme:



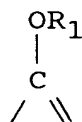


15 wherein A, B', D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above.

The conversion from the compound (Id) to the compound (If) can be effected under conditions similar to those employed in the conversion from the compound (VIII) to the compound (X) shown in Process 4(a).

Process 5:

20 Among the substituted benzothiazine derivatives (I), each compound (If) in which Z is a group represented by the following formula:



30 can be synthesized in accordance with the process which will be described hereinafter:

The target compound can be obtained, in accordance with the following reaction scheme, by reacting a compound represented by the formula (XV) with a compound represented by the formula (XVI) to obtain a compound represented by the formula (XVII), reacting the resulting compound with a compound represented by the formula (III) to obtain a compound represented by the formula (XXX), and then causing a nitrogen-containing compound represented by the formula (V) to act on the compound (XXX).

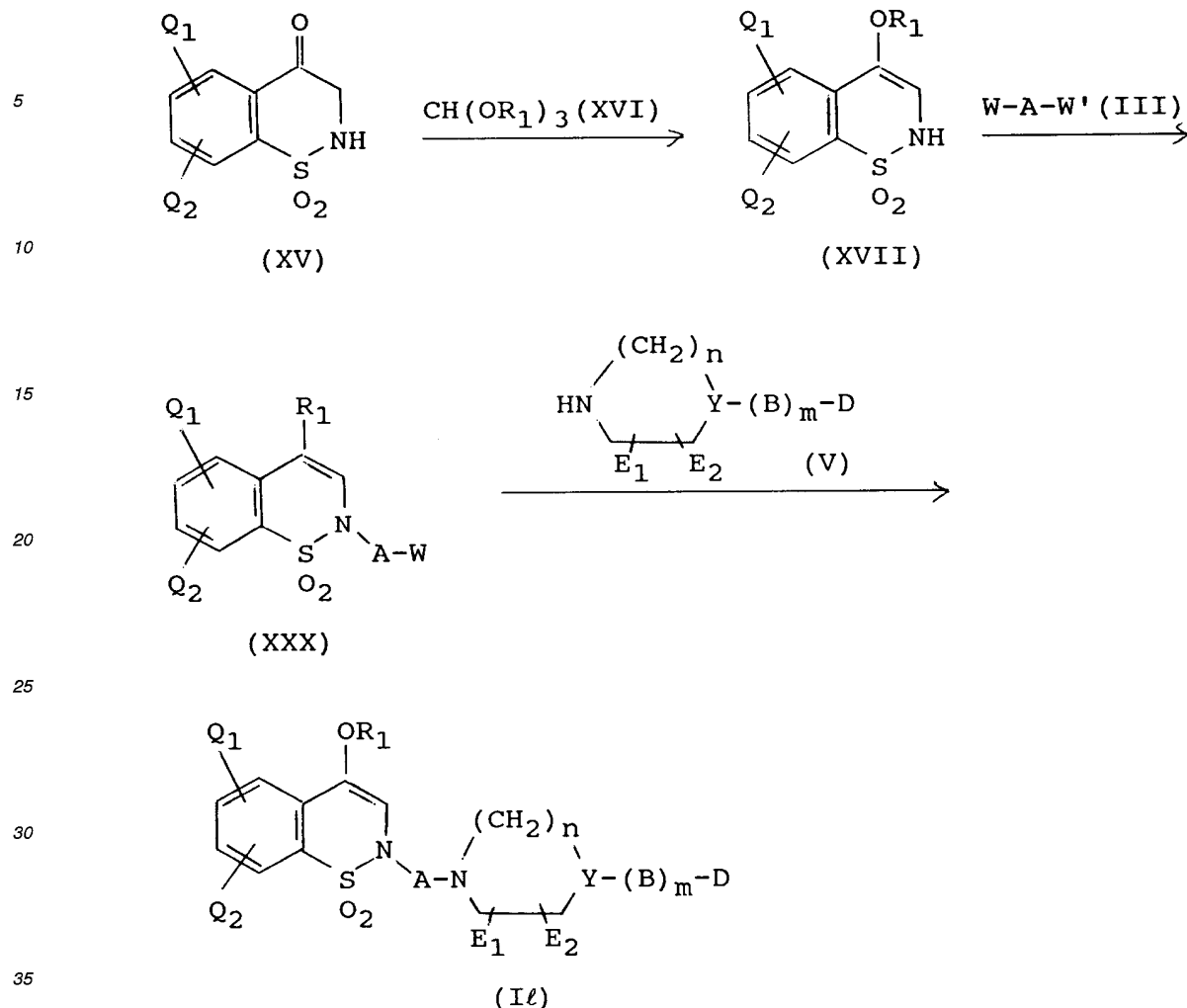
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wherein A, B, D, E₁, E₂, Q₁, Q₂, R₁, W, W', Y, m and n have the same meanings as defined above.

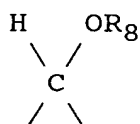
In the above reaction, the conversion from the compound (XV) to the compound (XVII) can be effected by causing the compound (XVI) to act on the compound (XV) in the presence of p-toluenesulfonic acid, boron trifluoride ethyl ether complex, Amberlite 15 or the like.

Examples of the solvent usable in the above reaction may include methanol, ethanol, propanol and butanol. The reaction can be conducted at -78°C to reflux temperature.

Further, the conversion from the compound (XVII) to the compound (Il) can be effected under conditions similar to those employed in the conversion from the compound (XXIV) to the compound (Ib) shown in Process 1(a).

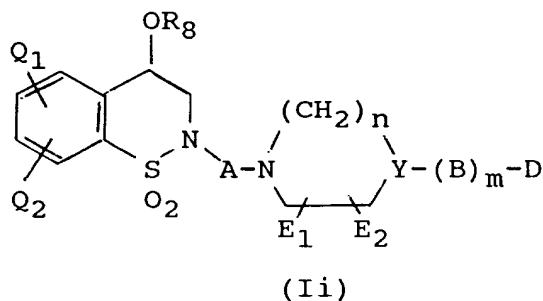
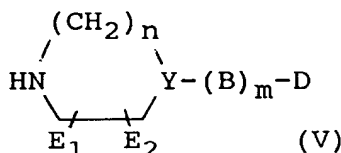
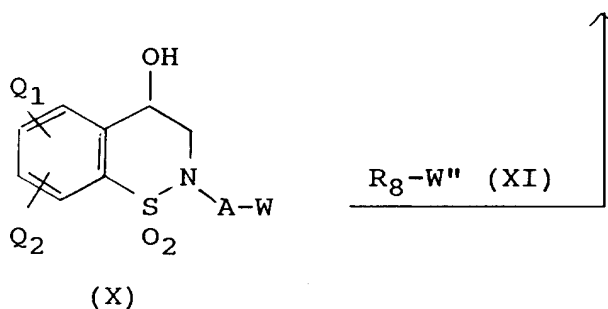
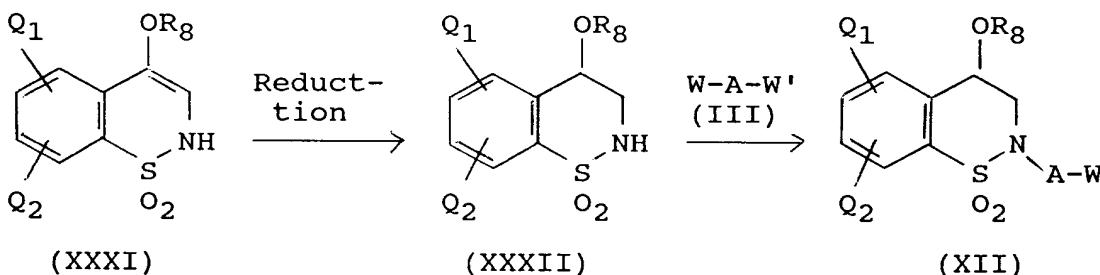
Process 6:

Among the substituted benzothiazine derivatives (I), each compound (Ii) in which Z is represented by the following formula:



can be synthesized in accordance with the process which will be described hereinafter.

The compound represented by the formula (II) can be obtained, in accordance with the following reaction scheme, (1) by reducing a compound represented by the formula (XXXI) to a compound represented by the formula (XXXII) and reacting the resulting compound with the compound represented by the formula (III), or (2) by reacting a compound represented by the formula (XI) with a compound represented by the formula (X) to obtain a compound (XII), and then reacting the resulting compound with a nitrogen-containing compound represented by the formula (V). In this case, it is desired to select a suitable process from the processes (1) and (2) according to the kind of group R_8 .



wherein A, B, D, E_1 , E_2 , Q_1 , Q_2 , R_8 , W, W' , W'' , Y, m and n have the same meanings as defined above.

In the above reaction, the conversion from the compound (XXXI) to the compound (XXXII) can be conducted by treating, in the presence of a catalyst such as palladium-carbon or platinum, the compound (XXXI) with hydrogen gas in a conventionally-employed solvent at -78°C to reflux temperature, preferably at room temperature. The conversion from the compound (XXXII) to the compound (XII) can be effected under conditions similar to those employed in the conversion from the compound (XXIV) to the compound (XXV) shown in Process 1(a).

The conversion from the compound (X) to the compound (XII) can be conducted by causing the compound (XI) to act on the compound (X) either after treatment of the compound (X) with an inorganic base or organic base or in the presence of such a base.

The group W'' in the compound (XI) is an eliminative substituent, and its examples include halogen atoms such as chlorine and bromine, alkylsulfonyloxy groups such as methanesulfonyloxy and arylsulfonyloxy groups such as p-toluenesulfonyloxy.

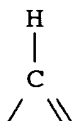
Further, exemplary inorganic or organic bases usable in the above reaction include sodium hydride, sodium bis(tri-

methylsilyl)amide, lithium diisopropylamide and potassium t-butoxide. Illustrative solvents usable in the present reaction include, tetrahydrofuran, dioxane, dimethylformamide, dimethylsulfoxide, N-methylpyrrolidone and toluene. The reaction may be conducted at -78°C to reflux temperature.

The conversion from the compound (XII) to the compound (Ii) can be effected under conditions similar to those employed upon conversion from the compound (XXV) to the compound (Ib) in Process 1(a).

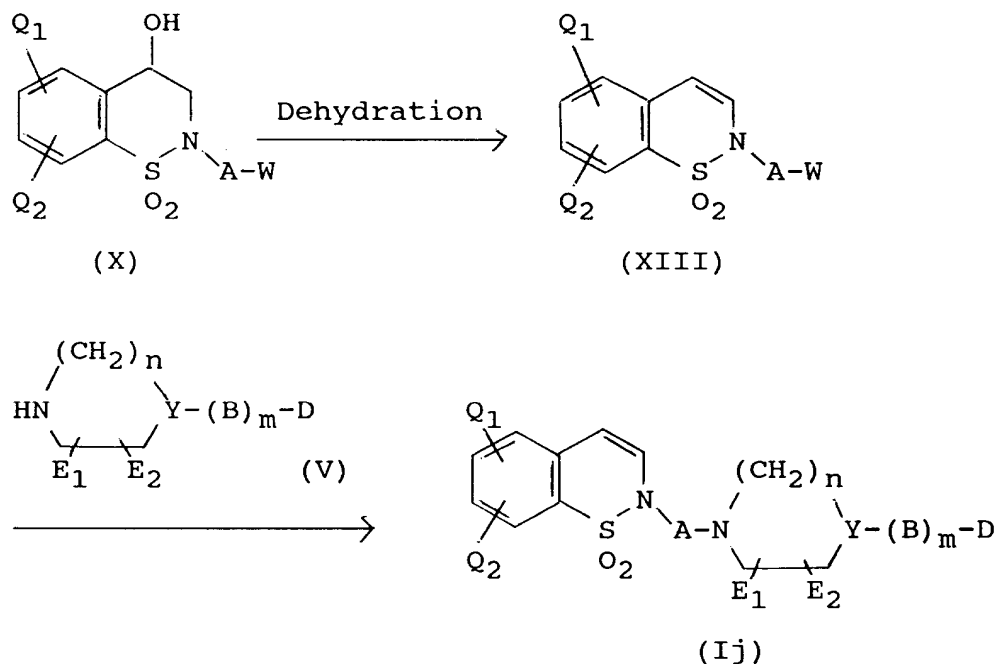
Process 7:

Among the substituted benzothiazine derivatives (I), each compound (Ij) in which Z is represented by the following formula:



can be synthesized in accordance with the process which will be described hereinafter.

The compound represented by the formula (Ij) can be obtained, in accordance with the following reaction scheme, by subjecting a compound represented by the formula (X) to dehydration to obtain a compound represented by the formula (XIII) and then causing a nitrogen-containing compound represented by the formula (V) to act on the resultant compound.



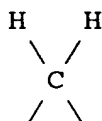
wherein A, B, D, E₁, E₂, Q₁, Q₂, W, Y, m and n have the same meanings as defined above.

In the above reactions, the conversion from the compound (X) to the compound (XIII) is conducted by causing methanesulfonyl chloride or p-toluenesulfonyl chloride and a base such as triethylamine, pyridine or collidine to act on the compound (X) in a solvent such as dichloromethane, chloroform or toluene and then treating the reaction product with the above base or silica gel at room temperature to reflux temperature.

Further, the conversion from the compound (XIII) to the compound (Ij) can be conducted under conditions similar to the conversion from the compound (XXV) to the compound (Ib) shown in Process I(a).

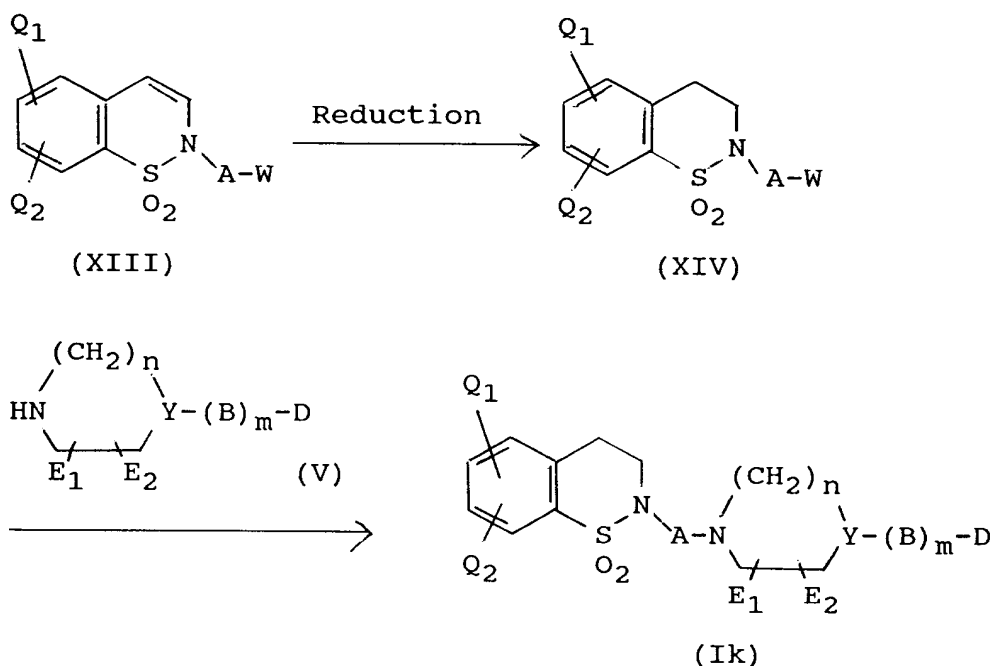
Process 8:

Among the substituted benzothiazine derivatives (I), each compound (Ik) in which Z is represented by the following formula:



can be synthesized in accordance with the process which will be described hereinafter.

The compound represented by the formula (Ik) can be obtained, in accordance with the following reaction scheme, by subjecting a compound represented by the formula (XIII) to reduction to obtain a compound represented by the formula (XIV) and then reacting the resultant compound with a nitrogen-containing compound represented by the formula (V).



wherein A, B, D, E_1 , E_2 , Q_1 , Q_2 , W, Y, m and n have the same meanings as defined above.

In the above reactions, the conversion from the compound (XIII) to the compound (XIV) can be conducted in a manner similar to the conversion from the compound (XXXI) to the compound (XXXII) in Process 6.

Further, the conversion from the compound (XIV) to the conversion (Ik) can be conducted under conditions similar to those employed in the conversion of the compound (XXV) to the compound (Ib) shown in Process 1(a).

The compounds (I) of the present invention obtained according to the above-described processes can each be reacted with one of various acids to convert the compound to its salt. The salt can be purified by a method such as recrystallization or column chromatography.

Exemplary acids usable to convert the substituted benzothiazine derivatives (I) to their salts include inorganic acids such as hydrochloric acid, nitric acid, sulfuric acid, phosphoric acid and hydrobromic acid; and organic acids such as maleic acid, fumaric acid, tartaric acid, lactic acid, citric acid, acetic acid, methanesulfonic acid, p-toluenesulfonic acid, adipic acid, palmitic acid and tannic acid.

As will be demonstrated later by tests, the substituted benzothiazine derivatives (I) and their salts according to the present invention, which can be obtained as described above, have a strong serotonin-2 blocking action and in addition, they have excellent selectivity to α_1 blocking action. Further, as a result of a toxicity test, they have been found to feature high safety. The compounds according to the present invention can therefore be used as therapeutics for circulatory diseases such as ischemic heart diseases, cerebrovascular disturbances and peripheral circulatory disturbances.

When the substituted benzothiazine derivative (I) according to this invention are used as drugs, they can be administered in an effective dose as they are. As an alternative, they can also be formulated into various preparation forms by known methods and then administered.

Exemplary preparation forms as drugs include orally administrable preparation forms such as tablets, powders, granules, capsules and syrups as well as parenterally administrable preparation forms such as injections and suppositories. Whichever preparation form is used, a known liquid or solid extender or carrier usable for the formulation of the preparation form can be employed.

Examples of such extender or carrier include polyvinylpyrrolidone, arabic gum, gelatin, sorbit, cyclodextrin, tragacanth gum, magnesium stearate, talc, polyethylene glycol, polyvinyl alcohol, silica, lactose, crystalline cellulose, sugar, starch, calcium phosphate, vegetable oil, carboxymethylcellulose, sodium laurylsulfate, water, ethanol, glycerin, mannitol, syrup, and the like.

When the compounds (I) according to the present invention are used as drugs, their dose varies depending on the administration purpose, the age, body weight and conditions of the patient to be administered, etc. In oral administration, the daily dose may generally be about 0.01-1,000 mg.

The present invention will next be described in further detail by the following examples and tests. It is however borne in mind that the present invention is not limited to the following examples and tests.

Example 1

Synthesis of 2-acetonyl-4-methoxy-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (Compound No. 1)

2.4 ml of 28% sodium methoxide solution in methanol (12 mmol) was added under ice cooling and stirring to a suspension of 2.34 g (11 mmol) of 4-methoxysaccharin in 20 ml of methanol, followed by stirring at 0°C for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was washed with ethyl ether and dried, whereby the sodium salt of 4-methoxysaccharin was obtained in the form of powder.

A solution of the thus-obtained sodium salt and 1.22 g (13.2 mmol) of chloroacetone in 20 ml of DMF was stirred at 90-95°C for 5 hours. The reaction mixture was concentrated under reduced pressure. A 3:1 mixed solvent of ethyl acetate and dichloromethane was added to the residue. The resulting solution was washed successively with water, a saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride:ethyl acetate = 50:1), whereby 2.78 g of the title compound were obtained (yield: 94%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 2

Synthesis of 2-acetonyl-4-chloro-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (Compound No. 2)

4.4 ml of 28% sodium methoxide solution in methanol (22 mmol) was added under ice cooling and stirring to a suspension of 4.36 g (20 mmol) of 4-chlorosaccharin in 40 ml of methanol, followed by stirring at 0°C for 30 minutes. The reaction mixture was treated as in Example 1, whereby the sodium salt of 4-chlorosaccharin was obtained in the form of powder.

A solution of the thus-obtained sodium salt and 2.21 g (24 mmol) of chloroacetone in 40 ml of DMF was stirred at 90-95°C for 15 hours. Post-treatments were conducted as in Example 1. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride:ethyl acetate = 30:1), whereby 4.70 g of the title compound were obtained (yield: 86%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 3

Synthesis of 2-acetonyl-5-methoxy-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (Compound No. 3)

3.2 ml of 28% sodium methoxide solution in methanol (16 mmol) was added under ice cooling and stirring to a suspension of 3.10 g (14.5 mmol) of 5-methoxysaccharin in 30 ml of methanol, followed by stirring at 0°C for 15 minutes. The reaction mixture was treated as in Example 1, whereby the sodium salt of 5-methoxysaccharin was obtained in the form of powder.

A solution of the thus-obtained sodium salt and 2.23 g (24.2 mmol) of chloroacetone in 30 ml of DMF was stirred at 90-95°C for 5 hours. The reaction mixture was concentrated under reduced pressure. A 1:4 mixed solvent of ethyl acetate and dichloromethane was added to the residue. The resulting solution was washed successively with water, a

saturated aqueous solution of sodium hydrogencarbonate and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride:ethyl acetate = 50:1), whereby 3.85 g of the title compound were obtained (yield: 98%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 4

Synthesis of 2-acetyl-5-chloro-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (Compound No. 4)

1.76 ml of 28% sodium methoxide solution in methanol (8.8 mmol) was added under ice cooling and stirring to a solution of 1.74 g (8 mmol) of 5-chlorosaccharin in 80 ml of methanol, followed by stirring at room temperature for 20 minutes. The reaction mixture was treated as in Example 1, whereby the sodium salt of 5-chlorosaccharin was obtained in the form of powder.

A solution of the thus-obtained sodium salt and 669 μ l (8.4 mmol) of chloroacetone in 7 ml of DMF was stirred at 100°C for 15 hours. The reaction mixture was concentrated under reduced pressure. To the residue was added water, and extracted twice with chloroform. Organic layers were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: chloroform), whereby 1.38 g of the title compound were obtained (yield: 63%). Although that compound was sufficiently pure, it can be recrystallized from methanol as needed.

Example 5

Synthesis of 2-acetyl-6-methoxy-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (Compound No. 5)

2 ml of 28% sodium methoxide solution in methanol (10 mmol) was added under ice cooling and stirring to a suspension of 1.9 g (9 mmol) of 6-methoxysaccharin in 18 ml of methanol, followed by stirring at 0°C for 15 minutes. The reaction mixture was treated as in Example 1, whereby the sodium salt of 6-methoxysaccharin was obtained in the form of powder.

A solution of the thus-obtained sodium salt and 1.39 g (15 mmol) of chloroacetone in 18 ml of DMF was stirred at 90-95°C for 20 hours. Post-treatments and purification were conducted as in Example 3, whereby 2.26 g of the title compound were obtained (yield: 93%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 6

Synthesis of 2-acetyl-6-chloro-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (Compound No. 6)

6.6 ml of 28% sodium methoxide solution in methanol (33 mmol) was added under ice cooling and stirring to a suspension of 6.54 g (30 mmol) of 6-chlorosaccharin in 60 ml of methanol, followed by stirring at 0°C for 15 minutes. The reaction mixture was treated as in Example 1, whereby the sodium salt of 6-chlorosaccharin was obtained in the form of powder.

A solution of the thus-obtained sodium salt and 3.30 g (36 mmol) of chloroacetone in 60 ml of DMF was stirred at 90-95°C for 12 hours. Post-treatments and purification were conducted as in Example 3, whereby 7.37 g of the title compound were obtained (yield: 89%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 7

Synthesis of 3-acetyl-5-methoxy-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Compound No. 7)

Compound No. 1 (2.42 g, 9 mmol) was added at 45°C to a solution of 414 mg (18 mmol) of sodium in 9 ml of ethanol, followed by stirring for 10 minutes. The reaction mixture was ice-cooled, to which 11.3 ml (22.6 mmol) of 2 N hydrochloric acid were added. Precipitated crystals were collected by filtration, washed with water and then dried, whereby 1.55 g of the title compound were obtained (yield: 64%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 8

Synthesis of 3-acetyl-5-chloro-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Compound No. 8)

Compound No. 2 (4.10 g, 15 mmol) was added at 50°C to a solution of 690 mg (30 mmol) of sodium in 15 ml of ethanol, followed by stirring for 10 minutes. The reaction mixture was ice-cooled, to which 18.7 ml (37.4 mmol) of 2 N hydrochloric acid were added. Precipitated crystals were collected by filtration, washed with water and then dried, whereby 3.00 g of the title compound were obtained (yield: 73%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 9

Synthesis of 3-acetyl-6-methoxy-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Compound No. 9)

Compound No. 3 (3.50 g, 13 mmol) was added at 50°C to a solution of 600 mg (26 mmol) of sodium in 13 ml of ethanol, followed by stirring for 10 minutes. The reaction mixture was ice-cooled, to which 15 ml (30 mmol) of 2 N hydrochloric acid were added. Precipitated crystals were collected by filtration, washed with water and then dried, whereby 2.90 g of the title compound were obtained (yield: 83%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 10

Synthesis of 3-acetyl-6-chloro-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Compound No. 10)

Compound No. 4 (1.26 g, 4.6 mmol) was added at 40°C to a solution of 212 mg (9.2 mmol) of sodium in 4.1 ml of ethanol, followed by stirring at 50-55°C for 5 minutes. The reaction mixture was ice-cooled, to which 5.75 ml (11.5 mmol) of 2 N hydrochloric acid were added. Precipitated crystals were collected by filtration, washed with 50% water-ethanol and then dried, whereby 1.15 g of the title compound were obtained (yield: 91%). Although that compound was sufficiently pure, it can be recrystallized from ethanol-water as needed.

Example 11

Synthesis of 3-acetyl-7-methoxy-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Compound No. 11)

Compound No. 5 (2.15 g, 8 mmol) was added at 45°C to a solution of 368 mg (16 mmol) of sodium in 7.2 ml of ethanol, followed by stirring for 10 minutes. The reaction mixture was ice-cooled, to which 10 ml (20 mmol) of 2 N hydrochloric acid were added. Precipitated crystals were collected by filtration, washed with water and then dried, whereby 1.70 g of the title compound were obtained (yield: 81%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 12

Synthesis of 3-acetyl-7-chloro-2H-1,2-benzothiazin-4(3H)-one 1,1-dioxide (Compound No. 12)

Compound No. 6 (6.84 g, 25 mmol) was added at 45°C to a solution of 1.15 g (50 mmol) of sodium in 22.5 ml of ethanol, followed by stirring for 10 minutes. The mixture was ice-cooled, to which 32 ml (64 mmol) of 2 N hydrochloric acid were added. Precipitated crystals were collected by filtration, washed with water and then dried, whereby 6.18 g of the title compound were obtained (yield: 90%). Although that compound was sufficiently pure, it can be recrystallized from ethanol-water as needed.

Example 13

Synthesis of 5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 13)

A solution of 935 mg (3.4 mmol) of Compound No. 7, 1.05 g (17 mmol) of ethylene glycol and 65 mg (0.34 mmol) of p-toluenesulfonic acid monohydrate in 30 ml of benzene was refluxed in a vessel equipped with a Dean & Stark water separator. Seventy (70) hours later, 1.05 g (17 mmol) of ethylene glycol were added, followed by further reflux for 24 hours. The solvent was concentrated to 15 ml under reduced pressure and crystals were collected by filtration. They were recrystallized from acetonitrile, whereby 590 mg of the title compound were obtained (yield: 64%).

Example 14

Synthesis of 5-chloro-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 14)

5 A solution of 2.73 g (10 mmol) of Compound No. 8, 3.10 g (50 mmol) of ethylene glycol and 190 mg (1 mmol) of p-toluenesulfonic acid monohydrate in 100 ml of benzene was refluxed in a vessel equipped with a Dean & Stark water separator. Eighty-four (84) hours later, 3.10 g (50 mmol) of ethylene glycol and 190 mg (1 mmol) of p-toluenesulfonic acid monohydrate were added, followed by further reflux for 84 hours. The reaction mixture was concentrated under reduced pressure, ethyl acetate was added to the residue, and crystals were collected by filtration. They were recrystallized from acetonitrile, whereby 1.00 g of the title compound was obtained (yield: 36%).

Example 15

Synthesis of 6-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 15)

15 A solution of 2.70 g (10 mmol) of Compound No. 9, 3.10 g (50 mmol) of ethylene glycol and 190 mg (1 mmol) of p-toluenesulfonic acid monohydrate in 30 ml of benzene was refluxed for 140 hours in a vessel equipped with a Dean & Stark water separator. Ethyl acetate was added to the reaction mixture. The resultant mixture was washed successively with a saturated aqueous solution of sodium hydrogencarbonate, water and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 1:2) and then recrystallized from acetonitrile, whereby 1.00 g of the title compound was obtained (yield: 37%).

Example 16

Synthesis of 6-chloro-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 16)

25 A solution of 4.70 g (17 mmol) of Compound No. 10, 5.30 g (85 mmol) of ethylene glycol and 323 mg (1.7 mmol) of p-toluenesulfonic acid monohydrate in 50 ml of benzene was refluxed in a vessel equipped with a Dean & Stark water separator. One hundred and forty-four (144) hours later, 930 mg (15 mmol) of ethylene glycol were added, followed by further reflux for 20 hours. Post-treatments were conducted as in Example 15. The residue was recrystallized from ethyl acetate-hexane, whereby 2.07 g of the title compound were obtained (yield: 44%).

Example 17

Synthesis of 7-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 17)

35 A solution of 1.70 g (6.3 mmol) of Compound No. 11, 2.00 g (32 mmol) of ethylene glycol and 60 mg (0.31 mmol) of p-toluenesulfonic acid monohydrate in 15 ml of benzene was refluxed in a vessel equipped with a Dean & Stark water separator. One hundred and forty-four (144) hours later, 465 mg (7.5 mmol) of ethylene glycol were added, followed by further reflux for 20 hours. Post-treatments were conducted as in Example 15. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride: ethyl acetate = 40:1), whereby 314 mg of the title compound were obtained (yield: 18%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 18

Synthesis of 7-chloro-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 18)

50 A solution of 5.48 g (20 mmol) of Compound No. 12, 6.2 g (100 mmol) of ethylene glycol and 125 mg (0.67 mmol) of p-toluenesulfonic acid monohydrate in 50 ml of benzene was refluxed in a vessel equipped with a Dean & Stark water separator. Two hundred and forty (240) hours later, 2.25 g (37.5 mmol) of ethylene glycol were added, followed by further reflux for 20 hours. Post-treatments and purification were conducted as in Example 17, whereby 1.77 g of the title compound were obtained (yield: 32%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 19

Synthesis of 5-chloro-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide (Compound No. 19)

5 3 N hydrochloric acid (10 mL, 30 mmol) was added to a suspension of 414 mg (1.5 mmol) of Compound No. 14 in 10 mL of methanol, followed by reflux for 70 minutes. The reaction mixture was concentrated under reduced pressure and precipitated crystals were collected by filtration. Those crystals were dissolved in ethyl acetate. The resulting solution was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and then concentrated under reduced pressure, whereby 362 mg of the title compound were obtained (yield: 94%). Although that
10 compound was sufficiently pure, it can be recrystallized from ethanol as needed.

Example 20

Synthesis of 5-chloro-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide (Compound No. 20)

15 Boron trifluoride-ether complex (62 μ L, 0.5 mmol) was added under ice cooling and stirring to a suspension of 232 mg (1 mmol) of Compound No. 19 and 252 μ L (3 mmol) of 1,2-ethanedithiol in 5 mL of methylene chloride. The resultant mixture was stirred at 0°C for 70 minutes and then at room temperature. Twenty-four (24) hours later, 31 μ L (0.25 mmol) of boron trifluoride-ether complex were added and seven (7) hours later, 63 μ L (0.75 mmol) of 1,2-ethanedithiol and 31
20 μ L (0.25 mmol) of boron trifluoride were added further, followed by stirring for 65 hours.

An aqueous solution of potassium carbonate was added to the reaction mixture, and the mixture so obtained was extracted twice with methylene chloride. Organic layers were washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride: methanol = 30:1), whereby 223 mg of the title compound were obtained (yield: 72%). Although that compound was sufficiently pure, it can be recrystallized from chloro-
25 form-hexane as needed.

Example 21

30 Synthesis of 2-(2-chloroethyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 21)

A solution of 190 mg (0.7 mmol) of Compound No. 13 in 5 mL of DMF was added under ice cooling and stirring to a suspension of 31 mg (0.77 mmol) of 60% sodium hydride in 5 mL of DMF. After the reaction mixture was stirred at 0°C
35 for 1 hour and then at room temperature for 1 hour, the reaction mixture was ice-cooled. A solution of 201 mg (1.4 mmol) of 1-bromo-2-chloroethane in 5 mL of DMF was then added, followed by stirring at room temperature for 16 hours.

The reaction mixture was concentrated under reduced pressure and 50 mL of a 5% aqueous solution of citric acid were added to the residue. The resultant mixture was extracted three times with methylene chloride. Organic layers were washed successively with water and a saturated aqueous solution of sodium chloride, dried over anhydrous
40 sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 1:1), whereby 213 mg of the title compound were obtained (yield: 91%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 22

45 Synthesis of 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 22)

A suspension of 813 mg (3 mmol) of Compound No. 13, 945 mg (6 mmol) of 1-bromo-3-chloropropane and 828 mg
50 (6 mmol) of potassium carbonate in 15 mL of DMF was stirred at room temperature for 15 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure.

Ethyl acetate was added to the residue. The mixture so obtained was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica
55 gel column (eluent: methylene chloride:ethyl acetate = 50:1), whereby 1.03 g of the title compound were obtained (yield: 98%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 23

Synthesis of 5-chloro-2-(3-chloropropyl)-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 23)

A suspension of 551 mg (2 mmol) of Compound No. 14, 630 mg (4 mmol) of 1-bromo-3-chloropropane and 552 mg (4 mmol) of potassium carbonate in 10 ml of DMF was stirred at room temperature for 20 hours. Post-treatments and purification were conducted as in Example 22, whereby 698 mg of the title compound were obtained (yield: 99%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 24

Synthesis of 2-(3-chloropropyl)-6-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 24)

A suspension of 542 mg (2 mmol) of Compound No. 15, 471 mg (3 mmol) of 1-bromo-3-chloropropane and 552 mg (4 mmol) of potassium carbonate in 20 ml of acetone was refluxed for 8 hours. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure.

Ethyl acetate was added to the residue. The mixture so obtained was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 1:2), whereby 578 mg of the title compound were obtained (yield: 83%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 25

Synthesis of 6-chloro-2-(3-chloropropyl)-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 25)

A suspension of 550 mg (2 mmol) of Compound No. 16, 471 mg (3 mmol) of 1-bromo-3-chloropropane and 552 mg (4 mmol) of potassium carbonate in 20 ml of acetone was refluxed for 14 hours. Post-treatments and purification were conducted as in Example 24, whereby 735 mg of the title compound were obtained (yield: 99%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 26

Synthesis of 2-(3-chloropropyl)-7-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 26)

A suspension of 271 mg (1 mmol) of Compound No. 17, 236 mg (1.5 mmol) of 1-bromo-3-chloropropane and 276 mg (2 mmol) of potassium carbonate in 10 ml of acetone was refluxed for 10 hours. Post-treatments and purification were conducted as in Example 24, whereby 321 mg of the title compound were obtained (yield: 92%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 27

Synthesis of 7-chloro-2-(3-chloropropyl)-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 27)

A suspension of 825 mg (3 mmol) of Compound No. 18, 707 mg (4.5 mmol) of 1-bromo-3-chloropropane and 828 mg (6 mmol) of potassium carbonate in 30 ml of acetone was refluxed for 7 hours. Post-treatments were conducted as in Example 24 and the residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 1:1), whereby 1.08 g of the title compound were obtained (yield: 99%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 28

Synthesis of 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide (Compound No. 28)

4 N hydrochloric acid (4 mL, 16 mmol) was added to a solution of 430 mg (1.24 mmol) of Compound No. 22 in 4 mL of methanol, followed by reflux for 2 hours. The reaction mixture was concentrated under reduced pressure. The residue was added with ethyl acetate. The mixture so obtained was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride:ethyl acetate = 30:1), whereby 392 mg of the title compound were obtained (yield: 99%).

Example 29

Synthesis of 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide (Compound No. 29)

Boron trifluoride-ether complex (0.06 mL, 0.45 mmol) was added under ice cooling and stirring to a solution of 350 mg (1.15 mmol) of Compound No. 28 and 0.12 mL (1.4 mmol) of ethanedithiol in 4.5 mL of methylene chloride. The resultant mixture was stirred at 0°C for 1 hour and then at room temperature for 12 hours.

Ethyl acetate was added to the reaction mixture. The mixture so obtained was washed successively with a saturated aqueous solution of sodium hydrogencarbonate and a saturated solution of sodium chloride, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 1:2) and then recrystallized from ethyl acetate-hexane, whereby 383 mg of the title compound were obtained (yield: 87%).

Example 30

Synthesis of 2-[2-[4-(4-fluorophenyl)piperazin-1-yl]ethyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 30)

A suspension of 100 mg (0.3 mmol) of Compound No. 21, 108 mg (0.6 mmol) of 1-(4-fluorophenyl)piperazine and 90 mg (0.6 mmol) of sodium iodide in 15 mL of acetonitrile was refluxed for 24 hours.

The reaction mixture was concentrated under reduced pressure and 50 mL of a half-saturated aqueous solution of potassium carbonate were added to the residue. The mixture so obtained was extracted three times with ethyl acetate. Organic layers were washed successively with water and a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 3:1), whereby 106 mg of the title compound were obtained (yield: 74%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 31

Synthesis of 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 31)

A suspension of 173 mg (0.5 mmol) of Compound No. 22, 135 mg (0.75 mmol) of 1-(4-fluorophenyl)piperazine, 84 mg (1 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 mL of acetonitrile was refluxed for 18 hours.

The reaction mixture was concentrated under reduced pressure and a saturated aqueous solution of sodium hydrogencarbonate was added to the residue. The mixture so obtained was extracted twice with methylene chloride. Organic layers were dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: methylene chloride: methanol = 30:1), whereby 243 mg of the title compound were obtained (yield: 98%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 32

Synthesis of 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 32)

5

A suspension of 173 mg (0.5 mmol) of Compound No. 22, 194 mg (0.75 mmol) of 1-(4-hydroxyphenyl)piperazine hydrobromide, 168 mg (2 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 ml of acetonitrile was refluxed for 20 hours.

10

Post-treatments were conducted as in Example 31 and the residue was purified by chromatography on a silica gel column (eluent: methylene chloride: methanol = 20:1), whereby 191 mg of the title compound were obtained (yield: 78%). Although that compound was sufficiently pure, it can be recrystallized from 2-propanol as needed.

Example 33

15 Synthesis of 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 33)

20

A suspension of 173 mg (0.5 mmol) of Compound No. 22, 183 mg (0.75 mmol) of 4-(4-fluorobenzoyl)piperidine hydrochloride, 168 mg (2 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 ml of acetonitrile was refluxed for 18 hours. Post-treatments and purification were conducted as in Example 31, whereby 247 mg of the title compound were obtained (yield: 95%).

Example 34

25 Synthesis of 5-chloro-2-[3-[4-(4-fluorophenyl)-piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 34)

30

A suspension of 141 mg (0.4 mmol) of Compound No. 23, 108 mg (0.6 mmol) of 1-(4-fluorophenyl)piperazine, 67 mg (0.8 mmol) of sodium hydrogencarbonate and 120 mg (0.8 mmol) of sodium iodide in 8 ml of acetonitrile was refluxed for 16 hours. Post-treatments and purification were conducted as in Example 31, whereby 196 mg of the title compound were obtained (yield: 98%).

Example 35

35 Synthesis of 5-chloro-2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 35)

40

A suspension of 141 mg (0.4 mmol) of Compound No. 23, 155 mg (0.6 mmol) of 1-(4-hydroxyphenyl)piperazine hydrobromide, 134 mg (1.6 mmol) of sodium hydrogencarbonate and 120 mg (0.8 mmol) of sodium iodide in 8 ml of acetonitrile was refluxed for 17 hours. Post-treatments and purification were conducted as in Example 32, whereby 181 mg of the title compound were obtained (yield: 93%).

Example 36

45 Synthesis of 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-6-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 36)

50

A suspension of 173 mg (0.5 mmol) of Compound No. 24, 135 mg (0.75 mmol) of 1-(4-fluorophenyl)piperazine, 84 mg (1 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 ml of acetonitrile was refluxed for 15 hours. Post-treatments and purification were conducted as in Example 32, whereby 229 mg of the title compound were obtained (yield: 93%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 37

55

Synthesis of 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-6-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 37)

A suspension of 173 mg (0.5 mmol) of Compound No. 24, 182 mg (0.75 mmol) of 4-(4-fluorobenzoyl)piperidine

hydrochloride, 168 mg (2 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 mL of acetonitrile was refluxed for 15 hours. Post-treatments were conducted as in Example 31 and the residue was purified by chromatography on a silica gel column (eluent: methylene chloride: methanol = 15:1), whereby 241 mg of the title compound were obtained (yield: 93%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 38

Synthesis of 6-chloro-2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 38)

A suspension of 176 mg (0.5 mmol) of Compound No. 25, 135 mg (0.75 mmol) of 1-(4-fluorophenyl)piperazine, 84 mg (1 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 mL of acetonitrile was refluxed for 15 hours. Post-treatments and purification were conducted as in Example 32, whereby 206 mg of the title compound were obtained (yield: 83%).

Example 39

Synthesis of 6-chloro-2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 39)

A suspension of 176 mg (0.5 mmol) of Compound No. 25, 182 mg (0.75 mmol) of 4-(4-fluorobenzoyl)piperidine hydrochloride, 168 mg (2 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 mL of acetonitrile was refluxed for 15 hours. Post-treatments and purification were conducted as in Example 32, whereby 211 mg of the title compound were obtained (yield: 80%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 40

Synthesis of 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-7-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 40)

A suspension of 104 mg (0.3 mmol) of Compound No. 26, 81 mg (0.45 mmol) of 1-(4-fluorophenyl)piperazine, 51 mg (0.6 mmol) of sodium hydrogencarbonate and 90 mg (0.6 mmol) of sodium iodide in 6 mL of acetonitrile was refluxed for 18 hours. Post-treatments and purification were conducted as in Example 31, whereby 138 mg of the title compound were obtained (yield: 94%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 41

Synthesis of 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-7-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 41)

A suspension of 104 mg (0.3 mmol) of Compound No. 26, 109 mg (0.45 mmol) of 4-(4-fluorobenzoyl)piperidine hydrochloride, 101 mg (1.2 mmol) of sodium hydrogencarbonate and 90 mg (0.6 mmol) of sodium iodide in 6 mL of acetonitrile was refluxed for 18 hours. Post-treatments and purification were conducted as in Example 32, whereby 140 mg of the title compound were obtained (yield: 90%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 42

Synthesis of 7-chloro-2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 42)

A suspension of 160 mg (0.45 mmol) of Compound No. 27, 135 mg (0.75 mmol) of 1-(4-fluorophenyl)piperazine, 84 mg (2 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 mL of acetonitrile was refluxed for 15 hours. Post-treatments and purification were conducted as in Example 31, whereby 194 mg of the title compound were obtained (yield: 78%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 43

Synthesis of 7-chloro-2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 43)

A suspension of 160 mg (0.45 mmol) of Compound No. 27, 182 mg (0.75 mmol) of 4-(4-fluorobenzoyl)-piperidine hydrochloride, 168 mg (2 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 ml of acetonitrile was refluxed for 15 hours. Post-treatments and purification were conducted as in Example 32, whereby 179 mg of the title compound were obtained (yield: 68%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

Example 44

Synthesis of 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide (Compound No. 44)

A suspension of 190 mg (0.5 mmol) of Compound No. 29, 135 mg (0.75 mmol) of 1-(4-fluorophenyl)piperazine, 84 mg (1 mmol) of sodium hydrogencarbonate and 150 mg (1 mmol) of sodium iodide in 10 ml of acetonitrile was refluxed for 18 hours. Post-treatments and purification were conducted as in Example 31, whereby 223 mg of the title compound were obtained (yield: 90%). Although that compound was sufficiently pure, it can be recrystallized from methanol as needed.

Example 45

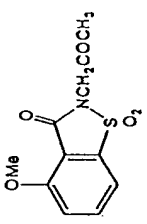
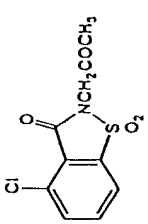
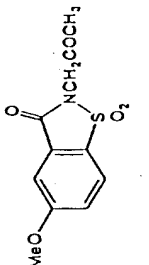
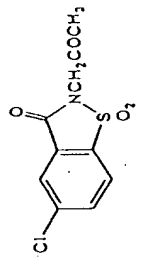
Synthesis of 5-chloro-2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide (Compound No. 45)

A solution of 154 mg (0.5 mmol) of Compound No. 20 in 1.5 ml of DMF was added under ice cooling and stirring to a suspension of 22 mg (0.55 mmol) of 60%-sodium hydride in 3 ml of DMF, followed by stirring at 0°C for 30 minutes and then at room temperature for 30 minutes. The reaction mixture was then cooled down to 0°C, to which a solution of 193 mg (0.75 mmol) of 1-(3-chloropropyl)-4-(4-fluorophenyl)piperazine in 1.5 ml of DMF was added. The resulting mixture was stirred at room temperature for 24 hours.

A 3:1 (by volume) mixed solvent of ethyl acetate and benzene was added to the reaction mixture. An organic layer was washed successively with a half-saturated aqueous solution of sodium hydrogencarbonate, water and a saturated solution of sodium chloride, dried over anhydrous sodium sulfate, and then concentrated under reduced pressure. The residue was purified by chromatography on a silica gel column (eluent: ethyl acetate:hexane = 1:2 → 1:1 → 2:1), whereby 102 mg of the title compound were obtained (yield: 39%). Although that compound was sufficiently pure, it can be recrystallized from ethyl acetate-hexane as needed.

The structural formulas and physical properties of the compounds obtained in the above examples are summarized in Table 1 to Table 12.

Table 1

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) (Observation frequency) * | IR (cm^{-1}) (Measuring method) |
|---------------|---|--|--|---|
| 1 |  | Colorless needle crystals 147.5-148.5 °C (ethyl acetate -hexane) | (400MHz) 2.27(3H, s), 4.05(3H, s), 4.40(2H, s), 7.29(1H, d, J=7.9Hz), 7.49(1H, d, J=7.9Hz), 7.82(1H, t, J=7.9Hz) | (KBr) 1740, 1718 1599, 1582 1486, 1439 1283, 1221 1165, 1041 988, 867 798, 679 |
| 2 |  | Colorless prism crystals 179.0-181.0 °C (ethyl acetate -hexane) | (400MHz) 2.29(3H, s), 4.47(2H, s), 7.78-7.83(2H, m), 7.86(1H, m) | (KBr) 3092, 1750 1732, 1578 1452, 1348 1032, 1182 1005, 988 801, 699 |
| 3 |  | Colorless needle crystals 166.0-167.0 °C (ethyl acetate -hexane) | (270MHz) 2.28(3H, s), 3.96(3H, s), 4.45(2H, s), 7.33(1H, dd, J=2.6Hz, 8.6Hz), 7.51(1H, d, J=2.6Hz), 7.83(1H, d, J=8.6Hz) | (KBr) 1740, 1724 1610, 1484 1329, 1307 1186, 1013 829 |
| 4 |  | Pale yellow prism crystals 154.0-154.5 °C (methanol) | (270MHz) 2.29(3H, s), 4.47(2H, s), 7.82-7.93(2H, m), 8.06(1H, d, J=2.0Hz) | (KBr) 1751, 1734 1421, 1331 1298, 1186 1084, 818 |

*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 2

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|--------------------|--|---|---|
| 5 | | Colorless needle crystals 186.5-188.0 °C (ethyl acetate -hexane) | (270MHz) 2.28(3H, s), 3.98(3H, s), 4.44(2H, s), 7.29(1H, dd, J=2.6Hz, 8.6Hz), 7.37(1H, d, J=2.8Hz), 7.98(1H, d, J=8.6Hz) | (KBr) 1740, 1722 1600, 1494 1325, 1178 1020, 847 762, 689 668 |
| 6 | | Colorless needle crystals 184.5-185.0 °C (ethyl acetate -hexane) | (270MHz) 2.29(3H, s), 4.47(2H, s), 7.82(1H, dd, J=2.0Hz, 8.6Hz), 7.93(1H, d, J=2.0Hz), 8.03(1H, d, J=8.6Hz) | (KBr) 1750, 1723 1592, 1335 1198, 1097 1052, 1003 864, 670 |
| 7 | | Pale ochreous needle crystals 206.5-208.0 °C (ethyl acetate -hexane) | (400MHz) 2.41(3H, s), 4.00(3H, s), 5.89(1H, bs), 7.24(1H, d, J=7.9Hz), 7.50(1H, d, J=7.9Hz), 7.67(1H, t, J=7.9Hz), 15.41(1H, bs) | (KBr) 1605, 1580 1474, 1382 1190, 1175 1158, 1038 928, 800 716 |
| 8 | | Pale brown prism crystals 159.5-161.0 °C (ethyl acetate -hexane) | (400MHz) 2.42(3H, s), 5.84(1H, bs), 7.61(1H, t, J=7.9Hz), 7.73(1H, dd, J=1.1Hz, 7.9Hz), 7.82(1H, dd, J=1.1Hz, 7.9Hz), 15.72(1H, s) | (KBr) 3212, 1626 1577, 1540 1436, 1376 1334, 1181 1159, 926 798 |

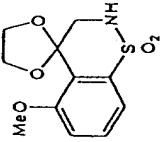
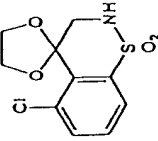
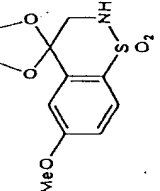
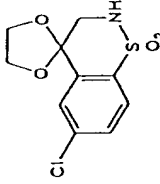
*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 3

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|--------------------|--|--|---|
| 9 | | Colorless needle crystals 187.0-188.0 °C (ethyl acetate -hexane) | (400MHz) 2.43(3H, s), 3.93(3H, s), 5.79(1H, bs), 7.19(1H, dd, J=2.6Hz, 8.6Hz), 7.57(1H, d, J=2.6Hz), 7.80(1H, d, J=8.6Hz), 15.10(1H, bs) | (KBr) 3178, 1561 1390, 1328 1236, 1179 1069, 906 834, 744 |
| 10 | | Yellow prism crystals 229.0-231.0 °C (ethanol-water) | (270MHz) 2.45(3H, s), 5.97(1H, s), 7.70(1H, dd, J=7.9Hz, 2.0Hz), 7.84(1H, d, J=7.9Hz), 8.11(1H, d, J=2.0Hz), 14.84(1H, s) | (KBr) 3194, 1591 1552, 1395 1327, 1181 1097, 912 726, 652 |
| 11 | | Pale ochreous needle crystals 162.5-163.5 °C (ethyl acetate -hexane) | (270MHz) 2.40(3H, s), 3.94(3H, s), 5.95(1H, s), 7.20(1H, dd, J=2.6Hz, 8.6Hz), 7.33(1H, d, J=2.6Hz), 8.06(1H, d, J=8.6Hz), 15.10(1H, bs) | (KBr) 1598, 1544 1495, 1386 1327, 1275 1230, 1177 1058, 1024 900, 840 |
| 12 | | Yellow needle crystals 216.0-217.5 °C (decomposed) (ethanol-water) | (270MHz) 2.44(3H, s), 6.01(1H, bs), 7.70(1H, dd, J=2.0Hz, 8.6Hz), 7.86(1H, d, J=2.0Hz), 8.08(1H, d, J=8.6Hz), 14.93(1H, bs) | (KBr) 3176, 1638 1589, 1538 1374, 1315 1178, 1102 836, 680 |

*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 4

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|---|---|---|--|
| 1 3 |  | Colorless needle crystals 254.0-256.0 °C (acetonitrile) | (400MHz)(DMSO-d ₆ /TMS) 3.54(2H, b), 3.84(3H, s), 4.04(2H, m), 4.18(2H, m), 7.25(1H, d, J=8.0Hz), 7.28(1H, d, J=8.0Hz), 7.55(1H, t, J=8.0Hz), 8.34(1H, b) | (KBr) 2980-2800 1591, 1469 1435, 1324 1276, 1207 1160, 1048 992, 946 919, 837 790, 742 |
| 1 4 |  | Colorless prism crystals 233.0-234.0 °C (acetonitrile) | (400MHz)(DMSO-d ₆ /TMS) 3.65(2H, d, J=5.8Hz), 4.16(2H, m), 4.29(2H, m), 7.61(1H, t, J=7.7Hz), 7.73(2H, d, J=7.7Hz), 8.59(1H, b) | (KBr) 3268, 3080 2908, 1582 1434, 1417 1322, 1271 1157, 1071 1048, 995 948, 830 799 |
| 1 5 |  | Colorless prism crystals 152.0-153.0 °C (acetonitrile) | (270MHz) 3.69(2H, d, J=7.9Hz), 3.87(3H, s), 4.16(2H, m), 4.26(2H, m), 5.11(1H, bt, J=7.9Hz), 6.99(1H, d, J=2.6Hz), 7.02(1H, dd, J=2.6Hz, 8.6Hz), 7.73(1H, d, J=8.6Hz) | (KBr) 3260, 1596 1486, 1448 1404, 1314 1244, 1155 1044, 951 872, 826 752, 699 |
| 1 6 |  | Colorless prism crystals 156.0-157.0 °C (ethyl acetate -hexane) | (270MHz) 3.71(2H, d, J=7.3Hz), 4.17(2H, m), 4.29(2H, m), 5.18(1H, m), 7.47~7.52(2H, m), 7.72(1H, d, J=8.2Hz) | (KBr) 3238, 1587 1430, 1329 1259, 1164 1100, 1040 946, 829 712 |

*: Measured in CDCl₃ with TMS as an internal standard unless otherwise specifically indicated.

Table 5

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|--------------------|--|---|---|
| 17 | | Colorless needle crystals 131.0-131.5 °C (ethyl acetate -hexane) | (270MHz) 3.70(2H, d, J=7.9Hz), 3.85(3H, s), 4.14(2H, m), 4.25(2H, m), 5.17(1H, m), 7.09(1H, dd, J=2.6Hz, 8.6Hz), 7.22(1H, d, J=2.6Hz), 7.45(1H, d, J=8.6Hz) | (KBr) 3186, 1608 1502, 1320 1242, 1151 1038, 829 742, 690 678 |
| 18 | | Colorless needle crystals 171.0-172.0 °C (ethyl acetate -hexane) | (270MHz) 3.71(2H, d, J=7.9Hz), 4.16(2H, m), 4.26(2H, m), 5.22(1H, m), 7.48(1H, d, J=8.6Hz), 7.53(1H, dd, J=2.0Hz, 8.6Hz), 7.76(1H, d, J=2.0Hz) | (KBr) 3191, 1592 1481, 1436 1327, 1160 1096, 1037 949, 920 830, 809 748, 692 |
| 19 | | Colorless prism crystals 183.0-185.5 °C (ethanol) | (400MHz) 4.36(2H, d, J=7.5Hz), 5.29(1H, b), 7.66(1H, t, J=8.0Hz), 7.74(1H, dd, J=1.2Hz, 8.0Hz), 7.84(1H, dd, J=1.2Hz, 8.0Hz) | (KBr) 3259, 1699 1405, 1340 1246, 1201 1176, 854 799 |
| 20 | | Colorless powdery crystals 228.5-229.5 °C (chloroform -hexane) | (400MHz) 3.46(2H, m), 3.69(2H, m), 3.98(2H, d, J=7.9Hz), 5.40(1H, b), 7.41(1H, t, J=8.0Hz), 7.62(1H, dd, J=1.3Hz, 8.0Hz), 7.80(1H, dd, J=1.3Hz, 8.0Hz) | (KBr) 3250, 1322 1177, 1070 792, 714 |

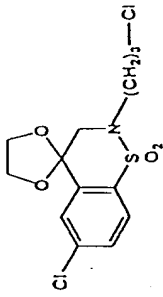
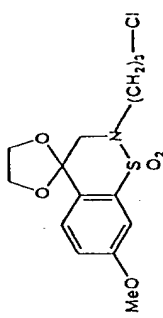
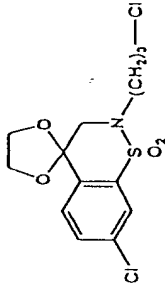
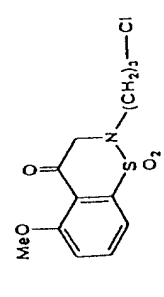
*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 6

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) [*] (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|--------------------|---|--|--|
| 2 1 | | Colorless prism crystals 172.0-173.0 °C (ethyl acetate -hexane) | (400MHz) 3.71(2H, m), 3.75(2H, m), 3.89(3H, s), 3.93(2H, s), 4.12(2H, m), 4.31(2H, m), 7.12(1H, d, J=8.0Hz), 7.41(1H, dd, J= 1.1Hz, 8.0Hz), 7.48(1H, t, J=8.0Hz) | (KBr) 1591, 1463 1431, 1324 1275, 1152 1090, 1048 998, 946 896, 843 794, 746 |
| 2 2 | | Colorless prism crystals 129.0-131.0 °C (ethyl acetate -hexane) | (400MHz) 2.10(2H, m), 3.60(2H, t, J=6.5Hz), 3.70(2H, t, J=6.2Hz), 3.85(2H, s), 3.89(3H, s), 4.13(2H, m), 4.31(2H, m), 7.11(1H, d, J=8.2Hz), 7.42(1H, d, J=8.2Hz), 7.48(1H, t, J=8.2Hz) | (KBr) 1590, 1464 1431, 1327 1276, 1154 1061, 1047 957, 942 795, 753 |
| 2 3 | | Colorless prism crystals 100.5-101.0 °C (ethyl acetate -hexane) | (400MHz) 2.10(2H, m), 3.61(2H, t, J=6.3Hz), 3.71(2H, t, J=6.1Hz), 3.90(2H, s), 4.21(2H, m), 4.44(2H, m), 7.46(1H, t, J=8.0Hz), 7.61(1H, dd, J=1.1Hz, 8.0Hz), 7.77(1H, dd, J=1.1Hz, 8.0Hz) | (KBr) 1582, 1335 1163, 1099 1056, 1037 950, 810 750 |
| 2 4 | | Colorless prism crystals 112.5-113.0 °C (ethyl acetate -hexane) | (270MHz) 2.10(2H, m), 3.60(2H, t, J=5.9Hz), 3.72(2H, t, J=5.9Hz), 3.86(3H, s), 3.89(2H, s), 4.18(2H, m), 4.28(2H, m), 6.96(1H, d, J=2.6Hz), 7.02(1H, dd, J= 2.6Hz, 9.2Hz), 7.73(1H, d, J=9.2Hz) | (KBr) 2977, 1608 1573, 1483 1424, 1326 1231, 1148 1047, 999 945, 895 818, 716 |

*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 7

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|---|--|---|---|
| 2 5 |  | Colorless prism crystals 94.0-94.5 °C (ethyl acetate -hexane) | (270MHz) 2.10(2H, m), 3.61(2H, t, J=6.6Hz), 3.71(2H, t, J=5.9Hz), 3.90(2H, s), 4.19(2H, m), 4.30(2H, m), 7.47~7.71(2H, m), 7.73(1H, d, J=7.3Hz) | (KBr) 2984, 2895 1588, 1460 1444, 1342 1241, 1151 1105, 1056 956, 950 810, 771 728, 703 |
| 2 6 |  | Colorless prism crystals 99.0-100.5 °C (ethyl acetate -hexane) | (270MHz) 2.11(2H, m), 3.61(2H, t, J=6.6Hz), 3.71(2H, t, J=5.9Hz), 3.86(3H, s), 3.88(2H, s), 4.15(2H, m), 4.26(2H, m), 7.09(1H, dd, J=2.6Hz, 8.6Hz), 7.21(1H, d, J=2.6Hz), 7.43(1H, d, J=8.6Hz) | (KBr) 2966, 2897 1607, 1500 1324, 1156 1034, 939 860, 828 709, 660 |
| 2 7 |  | Colorless prism crystals 87.5-88.5 °C (ethyl acetate -hexane) | (270MHz) 2.10(2H, m), 3.61(2H, t, J=6.6Hz), 3.71(2H, t, J=6.6Hz), 3.90(2H, s), 4.18(2H, m), 4.27(2H, m), 7.45(1H, d, J=8.6Hz), 7.53(1H, dd, J=2.0Hz, 8.6Hz), 7.76(1H, d, J=2.0Hz) | (KBr) 3066, 2956 1591, 1472 1448, 1328 1159, 1102 1046, 999 943, 827 696 |
| 2 8 |  | Pale yellow oil | 2.07(2H, m), 3.35(2H, t, J=6.7Hz), 3.63(2H, t, J=6.2Hz), 3.99(3H, s), 4.28(2H, s), 7.27(1H, d, J=7.6Hz), 7.48(1H, d, J=7.6Hz), 7.72(1H, t, J=7.6Hz) | (film) 2947, 1694 1588, 1567 1471, 1434 1338, 1280 1154, 1088 1042, 870 797, 735 |

*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 8

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|---------------|-----------------------|---|--|--|
| 2 9 | | Colorless needle crystals 138.5-139.0 °C (ethyl acetate -hexane) | (400MHz) 2.18(2H, m), 3.43(2H, m), 3.61(2H, m), 3.69(2H, t, J=6.4Hz), 3.74(2H, t, J=6.2Hz), 3.94(3H, s), 4.04(2H, s), 7.10(1H, dd, J= 1.4Hz, 8.0Hz), 7.41~7.49(2H, m) | (KBr) 2916, 1588 1464, 1434 1301, 1271 1164, 1141 1120, 1055 1032, 955 865, 793 762, 726 |
| 3 0 | | Colorless needle crystals 146.5-147.5 °C (ethyl acetate -hexane) | (400MHz) 2.66(4H, m), 2.71(2H, t, J=6.6Hz), 3.09(4H, m), 3.59(2H, t, J=6.6Hz), 3.88(3H, s), 3.95(2H, s), 4.11(2H, m), 4.30(2H, m), 6.85(2H, m), 6.94(2H, m), 7.10(1H, dd, J=1.3Hz, 8.0Hz), 7.40~7.53(2H, m) | (KBr) 1589, 1510 1372, 1333 1279, 1232 1154, 1052 996, 932 828, 752 738 |
| 3 1 | | Pale yellow prism crystals 174.0-175.0 °C (ethyl acetate -hexane) | (400MHz) 1.85(2H, m), 2.49(2H, t, J=7.1Hz), 2.61(4H, m), 3.12(4H, m), 3.50(2H, t, J=6.8Hz), 3.86(2H, s), 3.89(3H, s), 4.11(2H, m), 4.30(2H, m), 6.85~6.89(2H, m), 6.92~6.98(2H, m), 7.10(1H, d, J=8.0Hz), 7.43(1H, d, J= 8.0Hz), 7.48(1H, d, J=8.0Hz) | (KBr) 2822, 1589 1511, 1468 1322, 1274 1232, 1150 1053, 998 955, 832 740, 673 |
| 3 2 | | Pale ochreous needle crystals 191.0-192.5 °C (2-propanol) | (400MHz) 1.85(2H, m), 2.49(2H, t, J=7.1Hz), 2.61(4H, m), 3.08(4H, m), 3.50(2H, t, J= 6.8Hz), 3.85(2H, s), 3.88(3H, s), 4.10(2H, m), 4.29(2H, m), 6.75(2H, d, J= 8.8Hz), 6.84(2H, d, J=8.8Hz), 7.10(1H, d, J=8.0Hz), 7.43(1H, d, J= 8.0Hz), 7.48(1H, t, J=8.0Hz) | (KBr) 2900-2500 1589, 1514 1468, 1438 1332, 1276 1227, 1152 1051, 928 825, 741 |

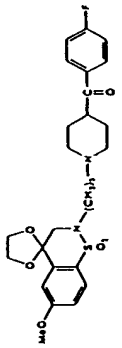
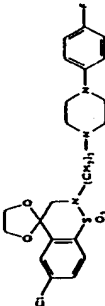
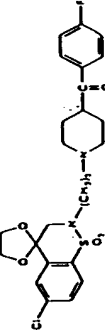
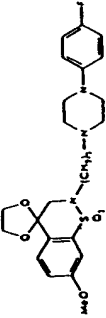
*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 9

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|--------------------|---|---|---|
| 3 3 | | Colorless amorphous | (400MHz) 1.80~1.90(6H, m), 2.09(2H, m), 2.46(2H, t, J=7.1Hz), 3.00(2H, m), 3.21(1H, m), 3.48(2H, t, J=6.8Hz), 3.86(2H, s), 3.89(3H, s), 4.13(2H, m), 4.30(2H, m), 7.09~7.16(3H, m), 7.42 ~7.50(2H, m), 7.95(2H, m) | (KBr) 2942, 1682 1598, 1508 1470, 1274 1153, 1050 952, 850 734, 672 |
| 3 4 | | Colorless prism crystals 186.0-187.0 °C (ethyl acetate -hexane) | (400MHz) 1.85(2H, m), 2.50(2H, t, J=7.1Hz), 2.62(4H, m), 3.12(4H, m), 3.51(2H, t, J=6.8Hz), 3.91(2H, s), 4.19(2H, m), 4.42(2H, m), 6.87(2H, m), 6.96(2H, m), 7.46(1H, t, J=7.9Hz), 7.60(1H, dd, J=1.2Hz, 7.9Hz), 7.77(1H, dd, J=1.2Hz, 7.9Hz) | (KBr) 2954, 2818 1506, 1333 1226, 1168 1041, 1001 967, 830 788, 737 |
| 3 5 | | Pale green needle crystals 212.5-213.5 °C (ethanol) | (400MHz) 1.85(2H, m), 2.50(2H, t, J=7.1Hz), 2.62(4H, m), 3.08(4H, m), 3.51(2H, t, J=6.8Hz), 3.91(2H, s), 4.19(2H, m), 4.42(2H, m), 6.75(2H, d, J=8.9Hz), 6.84(2H, d, J=8.9Hz), 7.45(1H, t, J=7.9Hz), 7.60(1H, dd, J=1.3Hz, 7.9Hz), 7.77(1H, dd, J=1.3Hz, 7.9Hz) | (KBr) 3079, 2966 2822, 1515 1439, 1336 1241, 1175 1162, 1050 996, 920 827, 742 |
| 3 6 | | Colorless prism crystals 110.5-111.5 °C (ethyl acetate -hexane) | (270MHz) 1.85(2H, m), 2.50(2H, t, J=7.3Hz), 2.62(4H, m), 3.12(4H, m), 3.50(2H, t, J=6.6Hz), 3.86(3H, s), 3.89(2H, s), 4.15(2H, m), 4.27(2H, m), 6.84~7.03(6H, m), 7.74(1H, d, J=8.6Hz) | (KBr) 2943, 2826 1597, 1512 1328, 1230 1152, 1042 947, 818 714 |

*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 10

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) [*] (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|------------|---|--|---|--|
| 3 7 |  | Colorless prism crystals 107.0-108.0 °C (ethyl acetate -hexane) | (270MHz) 1.72~1.90(6H, m), 2.09(2H, m), 2.47(2H, t, J=6.6Hz), 3.00(2H, m), 3.21(1H, m), 3.48(2H, t, J=6.6Hz), 3.86(3H, s), 3.90(2H, s), 4.18(2H, m), 4.27(2H, m), 6.95(1H, d, J=2.6Hz), 7.01(1H, dd, J=2.6Hz, 8.6Hz), 7.14(2H, m), 7.73(1H, d, J=8.6Hz), 7.97(2H, m) | (KBr) 2940, 1672 1599, 1480 1372, 1155 1045, 949 834, 734 708 |
| 3 8 |  | Pale yellow oil | (270MHz) 1.85(2H, m), 2.50(2H, t, J=7.3Hz), 2.61(4H, m), 3.12(4H, m), 3.51(2H, t, J=7.3Hz), 3.91(2H, s), 4.16(2H, m), 4.29(2H, m), 6.85~7.01(4H, m), 7.45~7.50(2H, m), 7.73(1H, d, J=7.9Hz) | (film) 2949, 2820 1510, 1456 1335, 1234 1158, 1051 952, 818 705 |
| 3 9 |  | Colorless needle crystals 149.5-150.5 °C (ethyl acetate -hexane) | (270MHz) 1.72~1.90(6H, m), 2.09(2H, m), 2.46(2H, t, J=6.6Hz), 2.95(2H, m), 3.21(1H, m), 3.50(2H, t, J=6.6Hz), 3.92(2H, s), 4.19(2H, m), 4.30(2H, m), 7.14(2H, m), 7.46~7.49(2H, m), 7.72(1H, d, J=9.2Hz), 7.97(2H, m) | (KBr) 2962, 1673 1595, 1505 1370, 1308 1236, 1156 1050, 948 853, 832 702 |
| 4 0 |  | Colorless needle crystals 140.0-140.5 °C (ethyl acetate -hexane) | (270MHz) 1.86(2H, m), 2.50(2H, t, J=6.6Hz), 2.62(4H, m), 3.12(4H, m), 3.51(2H, t, J=6.6Hz), 3.86(3H, s), 3.89(2H, s), 4.13(2H, m), 4.24(2H, m), 6.85~6.96(4H, m), 7.08(1H, dd, J=2.6Hz, 9.2Hz), 7.23(1H, d, J=2.6Hz), 7.41(1H, d, J=9.2Hz) | (KBr) 2950, 2827 1608, 1511 1326, 1274 1226, 1149 1031, 996 953, 879 823, 710 |

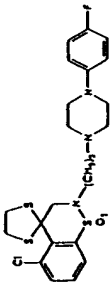
*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Table 11

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) [*] (Observation frequency) | IR (cm ⁻¹) (Measuring method) |
|------------|--------------------|--|--|---|
| 4 1 | | Colorless prism crystals 146.0-146.5 °C (ethyl acetate -hexane) | (270MHz) 1.78 ~ 1.88 (6H, m), 2.10 (2H, m), 2.47 (2H, t, J=6.6Hz), 3.00 (2H, m), 3.21 (1H, m), 3.50 (2H, t, J=6.6Hz), 3.86 (3H, s), 3.90 (2H, s), 4.15 (2H, m), 4.26 (2H, m), 7.06 ~ 7.17 (3H, m), 7.22 (1H, d, J=2.6Hz), 7.42 (1H, d, J=8.6Hz), 7.95 (2H, m) | (KBr) 2955, 2720 1676, 1500 1509, 1472 1326, 1148 998, 949 851, 735 700 |
| 4 2 | | Colorless needle crystals 134.0-135.0 °C (ethyl acetate -hexane) | (270MHz) 1.85 (2H, m), 2.50 (2H, t, J=6.6Hz), 2.61 (4H, m), 3.12 (4H, m), 3.52 (2H, t, J=6.6Hz), 3.90 (2H, s), 4.15 (2H, m), 4.26 (2H, m), 6.85 ~ 6.99 (4H, m), 7.43 (1H, d, J=8.6Hz), 7.52 (1H, dd, J=2.0Hz, 8.6Hz), 7.76 (1H, d, J=2.0Hz) | (KBr) 2832, 1509 1332, 1232 1162, 1104 1042, 944 825, 700 |
| 4 3 | | Colorless prism crystals 105.5-106.5 °C (ethyl acetate -hexane) | (270MHz) 1.78 ~ 1.89 (6H, m), 2.10 (2H, m), 2.46 (2H, t, J=6.6Hz), 2.99 (2H, m), 3.22 (1H, m), 3.50 (2H, t, J=6.6Hz), 3.92 (2H, s), 4.17 (2H, m), 4.27 (2H, m), 7.14 (2H, m), 7.44 (1H, d, J=8.6Hz), 7.52 (1H, dd, J=2.0Hz, 8.6Hz), 7.76 (1H, d, J=2.0Hz), 7.96 (2H, m) | (KBr) 2869, 2776 1676, 1592 1506, 1329 1224, 1165 1098, 1045 974, 836 696 |
| 4 4 | | Colorless plate crystals 129.0-130.0 °C (methanol) | (400MHz) 1.93 (2H, m), 2.53 (2H, t, J=7.1Hz), 2.63 (4H, m), 3.12 (4H, m), 3.41 (2H, m), 3.57 ~ 3.63 (4H, m), 3.94 (3H, s), 4.06 (2H, s), 6.86 (2H, m), 6.95 (2H, m), 7.09 (1H, dd, J=1.2Hz, 8.1Hz), 7.40 ~ 7.49 (2H, m) | (KBr) 2944, 2832 1586, 1510 1466, 1431 1336, 1274 1232, 1152 1051, 916 812, 791 703 |

*: Measured in CDCl₃ with TMS as an internal standard unless otherwise specifically indicated.

Table 12

| Comp'd No. | Structural formula | Property, Melting point (recrystallization solvent) | NMR (δ ppm) * (Observation frequency) | IR (cm^{-1}) (Measuring method) |
|---------------|---|---|---|---|
| 45 |  | Colorless prism crystals 119.5-121.0 °C (ethyl acetate -hexane) | (400MHz) 1.92(2H, quint, J=6.9Hz), 2.54(2H, t, J=6.9Hz), 2.62(4H, m), 3.12(4H, m), 3.46(2H, m), 3.64(2H, t, J=6.7Hz), 3.71(2H, m), 4.09(2H, s), 6.87(2H, m), 6.95(2H, m), 7.39(1H, t, J=8.0Hz), 7.59(1H, dd, J=1.4Hz, 8.0Hz), 7.83(1H, dd, J=1.4Hz, 8.0Hz) | (KBr) 2941, 2819 1511, 1436 1331, 1235 1166, 937 817, 776 712 |

*: Measured in CDCl_3 with TMS as an internal standard unless otherwise specifically indicated.

Example 46

Following the process described in Example 31 or Example 32 or a process similar to it, the following compounds can each be obtained using as a substituted benzothiazine derivative, besides 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal (Compound No. 22), 2-(2-chloroethyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal, 2-(4-chlorobutyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal, 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-

spiro-2'-(1',3'-dithiolane) 1,1-dioxide, 2-(2-chloroethyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide, 2-(4-chlorobutyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide, 2-(3-chloropropyl)-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(2-chloroethyl)-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(4-chlorobutyl)-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide, 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiane) 1,1-dioxide, 2-(3-chloropropyl)-4,4-bis(ethylthio)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-one 1,1-dioxide, 2-(3-chloropropyl)-4-hydroxyimino-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(2-chloroethyl)-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(4-chlorobutyl)-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-4,5-dimethoxy-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(2-chloroethyl)-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(4-chlorobutyl)-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-4-ethoxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 4-benzyloxy-2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide, 2-(3-chloropropyl)-5-methoxy-2H-1,2-benzothiazine 1,1-dioxide or 2-(3-chloropropyl)-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide and as a piperazine derivative or piperidine derivative, 1-phenyl-piperazine, 1-(2-fluorophenyl)piperazine, 1-(4-fluorophenyl)piperazine, 1-(4-hydroxyphenyl)piperazine, 1-(3-methoxyphenyl)piperazine, 1-(2-pyridyl)piperazine or 4-(4-fluorobenzoyl)piperidine.

Further, modifications to the substituted benzothiazine derivatives as raw materials and the treatments in the Examples make it possible to obtain corresponding compounds. For such modifications, the disclosure of PCT International Application No. PCT/JP94/02194 (now WO 95/18117) will be very useful.

- (1) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal
- (2) 2-[4-[4-(4-fluorophenyl)piperazin-1-yl]butyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal
- (3) 5-methoxy-2-[3-[4-(phenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal
- (4) 5-methoxy-2-[3-[4-(3-methoxyphenyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal
- (5) 5-methoxy-2-[3-[4-(2-pyridyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide ethylene acetal
- (6) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide
- (7) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide
- (8) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide
- (9) 2-[2-[4-(4-fluorophenyl)piperazin-1-yl]ethyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide
- (10) 2-[4-[4-(4-fluorophenyl)piperazin-1-yl]butyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide
- (11) 5-methoxy-2-[3-[4-(2-pyridyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiolane) 1,1-dioxide
- (12) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
- (13) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
- (14) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
- (15) 2-[2-[4-(4-fluorophenyl)piperazin-1-yl]ethyl]-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
- (16) 2-[4-[4-(4-fluorophenyl)piperazin-1-yl]butyl]-4,4,5-trimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
- (17) 4,4,5-trimethoxy-2-[3-[4-(2-pyridyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
- (18) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide
- (19) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide
- (20) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide
- (21) 2-[2-[4-(4-fluorophenyl)piperazin-1-yl]ethyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide
- (22) 2-[4-[4-(4-fluorophenyl)piperazin-1-yl]butyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide

dioxane) 1,1-dioxide

(23) 5-methoxy-2-[3-[4-(2-pyridyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dioxane) 1,1-dioxide

(24) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiane) 1,1-dioxide

(25) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiane) 1,1-dioxide

(26) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine-4-spiro-2'-(1',3'-dithiane) 1,1-dioxide

(27) 4,4-bis(ethylthio)-2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(28) 4,4-bis(ethylthio)-2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(29) 4,4-bis(ethylthio)-2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(30) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide

(31) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide

(32) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazin-4-one 1,1-dioxide

(33) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxyimino-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(34) 4-hydroxyimino-2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(35) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-4-hydroxyimino-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(36) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(37) 4-hydroxy-2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(38) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(39) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(40) 2-[2-[4-(4-fluorophenyl)piperazin-1-yl]ethyl]-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(41) 2-[4-[4-(4-fluorophenyl)piperazin-1-yl]butyl]-4-hydroxy-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(42) 4-hydroxy-5-methoxy-2-[3-[4-(2-pyridyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(43) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4,5-dimethoxy-2H-1,2-benzothiazine 1,1-dioxide

(44) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-4,5-dimethoxy-2H-1,2-benzothiazine 1,1-dioxide

(45) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-4,5-dimethoxy-2H-1,2-benzothiazine 1,1-dioxide

(46) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-4,5-dimethoxy-2H-1,2-benzothiazine 1,1-dioxide

(47) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(48) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(49) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(50) 2-[3-[4-(2-fluorophenyl)piperazin-1-yl]propyl]-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(51) 2-[2-[4-(4-fluorophenyl)piperazin-1-yl]ethyl]-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(52) 2-[4-[4-(4-fluorophenyl)piperazin-1-yl]butyl]-4,5-dimethoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(53) 4,5-dimethoxy-2-[2-[4-(2-pyridyl)piperazin-1-yl]propyl]-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(54) 4-ethoxy-2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(55) 4-ethoxy-2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(56) 4-ethoxy-2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(57) 4-benzyloxy-2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(58) 4-benzyloxy-2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

(59) 4-benzyloxy-2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

- (60) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-2H-1,2-benzothiazine 1,1-dioxide
 (61) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-2H-1,2-benzothiazine 1,1-dioxide
 (62) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-2H-1,2-benzothiazine 1,1-dioxide
 (63) 2-[3-[4-(4-fluorophenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
 (64) 2-[3-[4-(4-hydroxyphenyl)piperazin-1-yl]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide
 (65) 2-[3-[4-(4-fluorobenzoyl)piperidino]propyl]-5-methoxy-3,4-dihydro-2H-1,2-benzothiazine 1,1-dioxide

Test

With respect to the compounds of the present invention, their anti-serotonin (5-HT) action and anti- α_1 action were investigated by the testing methods which will be described below. The results of some representative compounds are shown in Table 13.

(1) Anti-serotonin action (anti-5-HT action)

The superior mesenteric artery of each Hartley male guinea pig (body weight: 300-500 g) was excised. A preparation cut in a helical form was suspended under 0.3 g load in a Magnus cylinder filled with the Tyrode solution which had been aerated with a gas mixture of 95% O₂ + 5% CO₂ and maintained at 37°C. Using an isometric transducer ("UL-10", manufactured by SHINKOH K.K.) and a pressure preamplifier ("DSA-605A", manufactured by SHINKOH K.K.), variations in tension were measured. The isometric tensions were recorded on a pen-writing recorder ("VP-6537A", manufactured by NATIONAL K.K.). Taking the contraction induced by 10⁻⁵ M serotonin (5-HT) as 100%, the percent contractions in the presence of each test drug at 10⁻⁷ and 10⁻⁶ M were determined as anti-5-HT action.

(2) Anti- α_1 action

The thoracic aorta of each Hartley male guinea pig (body weight: 300-500 g) was excised. A preparation cut in a helical form was suspended under 1 g load in a Magnus cylinder filled with the Tyrode solution which had been aerated with a gas mixture of 95% O₂ + 5% CO₂ and maintained at 37°C. Using an isometric transducer ("TB-612J", manufactured by NIHON KOHDEN) and a pressure preamplifier ("AP-620G", manufactured by NIHON KOHDEN), variations in tension were measured. The isometric tensions were recorded on a thermal pen-writing recorder ("WT-647G", manufactured by NIHON KOHDEN).

Taking the tonic contraction induced by 10⁻⁵ M norepinephrine (NE) as 100%, the percent contractions upon addition of each test drug at 10⁻⁸ and 10⁻⁷ M were determined as anti- α_1 action.

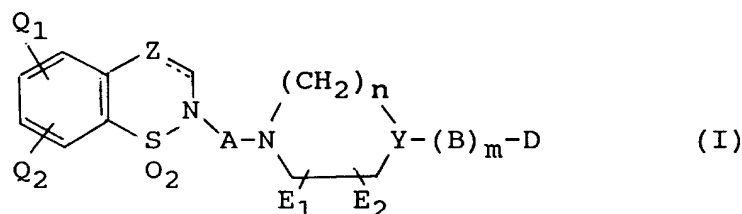
(Results)

Table 13

| Comp'd No. | Anti 5-HT action (% of Control) | | Anti α_1 action (% of Control) | |
|-----------------|------------------------------------|--------------------|--|--------------------|
| | 10 ⁻⁷ M | 10 ⁻⁶ M | 10 ⁻⁸ M | 10 ⁻⁷ M |
| 30 | 10.5 | NT | 99.3 | 96.1 |
| 31 | 5.6 | NT | 100 | 81.1 |
| 32 | 10.9 | NT | 100.9 | 98.6 |
| 33 | 17.1 | NT | 99.7 | 90.0 |
| 34 | 49.5 | NT | 98.3 | 89.3 |
| 35 | 23.5 | NT | 101.1 | 98.9 |
| 36 | 63.0 | 14.1 | 100.4 | 62.3 |
| 37 | 40.2 | 13.9 | 100.7 | 88.3 |
| 38 | 48.0 | 23.6 | 97.1 | 80.2 |
| 40 | 39.0 | 9.2 | 96.6 | 73.6 |
| 41 | 51.6 | 20.3 | 93.2 | 71.6 |
| 44 | 49.3 | NT | 97.9 | 13.0 |
| NT: Not tested. | | | | |

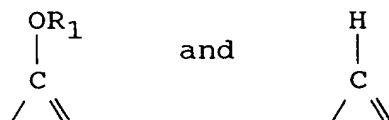
Claims

1. A substituted benzothiazine derivative represented by the following formula (I):

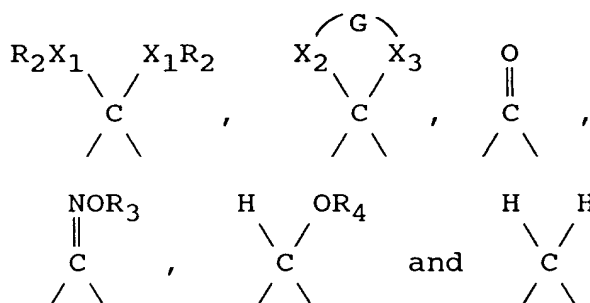


15 wherein the dashed line indicates the presence or absence of a bond and when the bond indicated by the dashed line is present,

Z represents one of the following groups:



in which R₁ represents a substituted or unsubstituted alkyl group or a substituted or unsubstituted aralkyl group but, when the bond indicated by the dashed line is absent, Z represents one of the following groups:



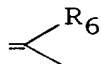
45 wherein R₂ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, R₃ represents a hydrogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, R₄ represents a hydrogen atom, a substituted or unsubstituted alkyl group or a substituted or unsubstituted aralkyl group, X₁, X₂ and X₃ each independently represents an oxygen atom or a sulfur atom, G represents an ethylene group with one or more of the hydrogen atoms thereof optionally substituted by a like number of halogen atoms and/or alkyl, aryl, aralkyl and/or alkylidene groups or a trimethylene group with one of more of the hydrogen atoms thereof optionally substituted by a like number of halogen atoms and/or alkyl, aryl, aralkyl and/or alkylidene groups,

50 Q₁ represents a hydrogen atom, a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aralkyloxy group,

55 Q₂ represents a hydroxyl group, a halogen atom, a substituted or unsubstituted alkyl group, a substituted or unsubstituted alkoxy group, a substituted or unsubstituted aralkyl group or a substituted or unsubstituted aralkyloxy group,

A represents a substituted or unsubstituted alkylene group, a substituted or unsubstituted alkenylene group or a substituted or unsubstituted alkynylene group,

Y represents CH, C= or a nitrogen atom; and, when Y represents CH, m stands for 0 or 1, n stands for 1 or 2, and B represents an oxygen atom, a sulfur atom, a carbonyl group, a sulfinyl group, a sulfonyl group, an alkylene group, an alkenylene group, a substituted or unsubstituted hydroxymethylene group, a group -CHR₅- in which R₅ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted cyclic or acyclic acetal group, when Y represents C=, m stands for 1, n stands for 1 or 2, and B represents:

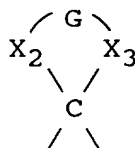


in which the double bond is linked to Y, R₆ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, but, when Y represents a nitrogen atom, m stands for 0 or 1, n stands for 2 or 3, and B represents a carbonyl group, a sulfonyl group, an alkylene group, an alkenylene group or a group -CHR₇- in which R₇ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group,

E₁ and E₂ each independently represents a hydrogen atom or a lower alkyl group, and

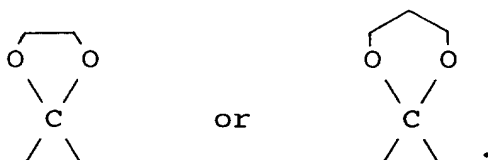
D represents a substituted or unsubstituted aromatic hydrocarbon group or a substituted or unsubstituted aromatic heterocyclic group; or a salt thereof.

2. A substituted benzothiazine derivative or a salt thereof according to claim 1, wherein in the formula (I), Z represents the following group:

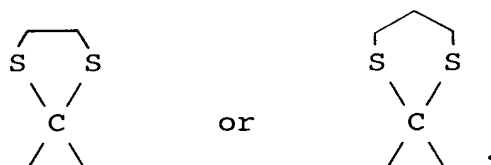


wherein G, X₂ and X₃ have the same meanings as defined above.

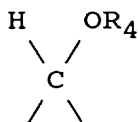
3. A substituted benzothiazine derivative or a salt thereof according to claim 1, wherein in the formula (I), Z represents the following group:



4. A substituted benzothiazine derivative or a salt thereof according to claim 1, wherein in the formula (I), Z represents the following group:

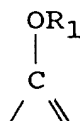


5. A substituted benzothiazine derivative or a salt thereof according to claim 1, wherein in the formula (I), Z represents the following group:



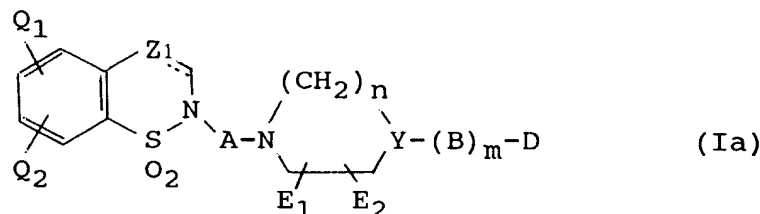
wherein R_4 has the same meaning as defined above.

6. A substituted benzothiazine derivative or a salt thereof according to claim 1, wherein in the formula (I), Z represents the following group:

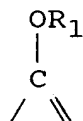


wherein R_1 has the same meaning as defined above.

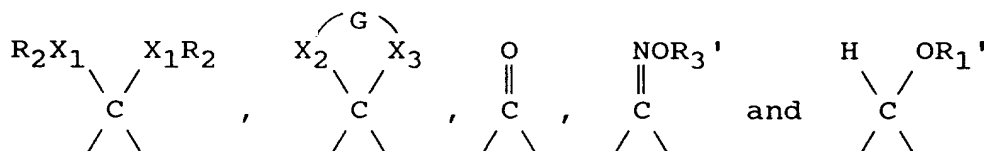
7. A substituted benzothiazine derivative or a salt thereof according to any one of claims 1, 2, 3, 4, 5 and 6, wherein in the formula (I), Q_1 represents a hydrogen atom and Q_2 represents a methoxy group.
8. A substituted benzothiazine derivative or a salt thereof according to any one of claims 1, 2, 3, 4, 5, 6 and 7, wherein in the formula (I), A represents an ethylene group or a trimethylene group.
9. A substituted benzothiazine derivative or a salt thereof according to any one of claims 1, 2, 3, 4, 5, 6, 7 and 8 wherein in the formula (I), Y represents CH, n stands for 2, B represents a carbonyl group, m stands for 0 or 1, and D represents a substituted or unsubstituted phenyl group.
10. A substituted benzothiazine derivative or a salt thereof according to any one of claims 1, 2, 3, 4, 5, 6, 7 or 8, wherein in the formula (I), Y represents a nitrogen atom, n stands for 2, m stands for 0, and D represents a substituted or unsubstituted phenyl group.
11. A substituted benzothiazine derivative or a salt thereof according to any one of claims 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10, wherein in the formula (I), E_1 and E_2 each represents a hydrogen atom.
12. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ia):



wherein the dashed line indicates the presence or absence of a bond and, when the dashed line is present, Z_1 represents the following group:

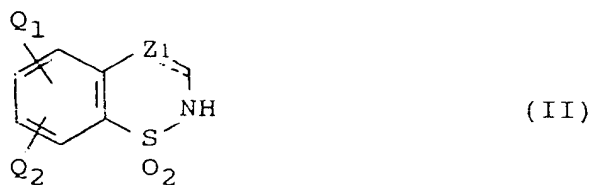


in which R_1 has the same meaning as defined above but, when the dashed line is absent, Z_1 represents one of the following groups:



in which R_1' represents a substituted or unsubstituted alkyl group, R_3' represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group and G , R_2 , X_1 , X_2 and X_3 have the same meanings as defined above, and A , B , D , E_1 , E_2 , Q_1 , Q_2 , Y , m and n have the same meanings as defined above, which comprises:

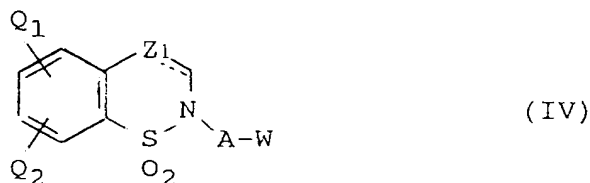
reacting a compound, which is represented by the following formula (II):



wherein Q_1 , Q_2 and Z_1 have the same meanings as defined above, with a compound represented by the following formula (III):

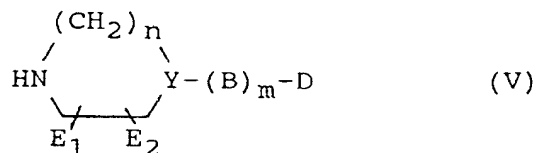


wherein A has the same meaning as defined above and W and W' may be the same or different and individually represent a substituent easily replaceable with an amino group, to obtain a compound represented by the following formula (IV):



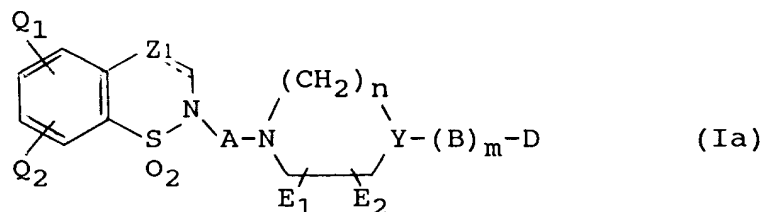
wherein A , Q_1 , Q_2 , W and Z_1 have the same meanings as defined above; and

then reacting the resulting compound with a nitrogen-containing compound represented by the following formula (V):

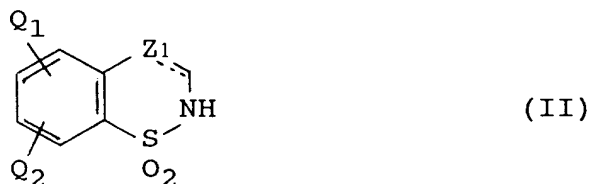


wherein B, D, E₁, E₂, Y, m and n have the same meanings as defined above.

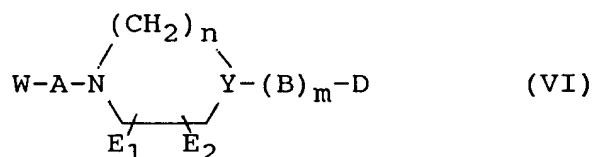
13. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ia):



wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, Z₁, m and n have the same meanings as defined above, which comprises:
reacting a compound, which is represented by the following formula (II):

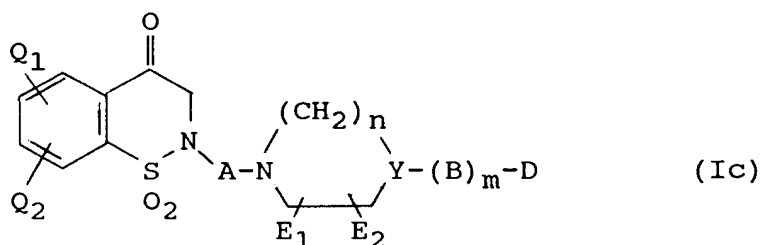


wherein Q₁, Q₂ and Z₁ have the same meanings as defined above, with a nitrogen-containing compound represented by the following formula (VI):



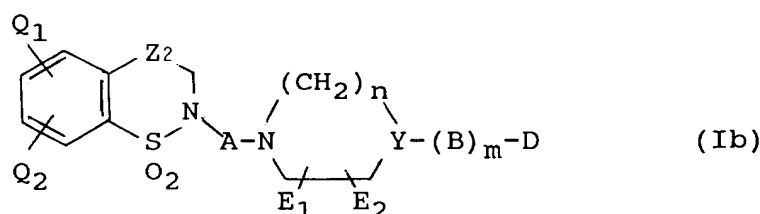
wherein A, B, D, E₁, E₂, W, Y, m and n have the same meanings as defined above.

14. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ic):



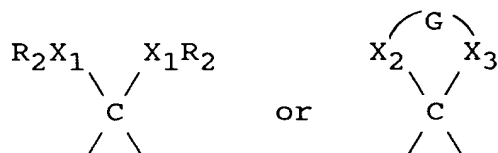
wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above, which comprises converting Z₂ of a substituted benzothiazine derivative to a carbonyl group, said derivative being represented by the following formula (Ib):

15



wherein Z₂ represents the following group:

30

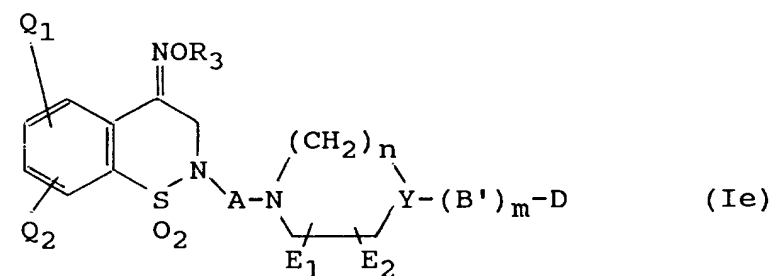


in which G, R₂, X₁, X₂ and X₃ have the same meanings as defined above, and A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above.

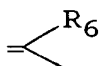
40

15. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ie):

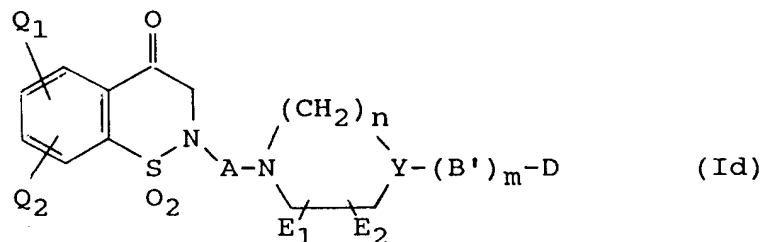
45



wherein, when Y represents CH, B' represents an oxygen atom, a sulfur atom, a sulfinyl group, a sulfonyl group, an alkylene group, an alkenylene group, a substituted or unsubstituted hydroxymethylene group, a group -CHR₅- in which R₅ represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, or a substituted or unsubstituted cyclic or acyclic acetal group, when Y represents C=, B' represents the following group:



in which the double bond is linked to Y, R_6 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, but, when Y represents a nitrogen atom, B' represents a carbonyl group, a sulfonyl group, an alkylene group, an alkenylene group or a group $-CHR_7-$ in which R_7 represents a substituted or unsubstituted alkyl group, a substituted or unsubstituted aryl group or a substituted or unsubstituted aralkyl group, and A, D, E_1 , E_2 , Q_1 , Q_2 , Y, m and n have the same meanings as defined above, which comprises reacting a substituted benzothiazine derivative, which is represented by the following formula (Id):

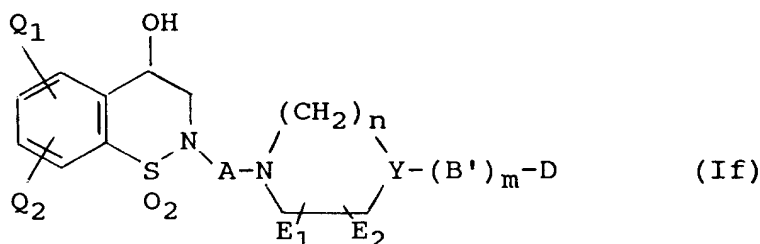


wherein A, B' , D, E_1 , E_2 , Q_1 , Q_2 , Y, m and n have the same meanings as defined above, with a hydroxylamine represented by the following formula (VII):

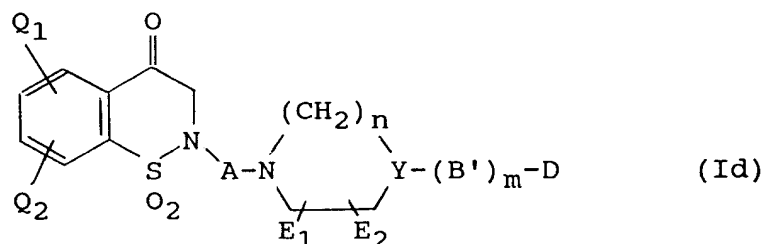


wherein R_3 has the same meaning as defined above or with a derivative thereof.

16. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (If):

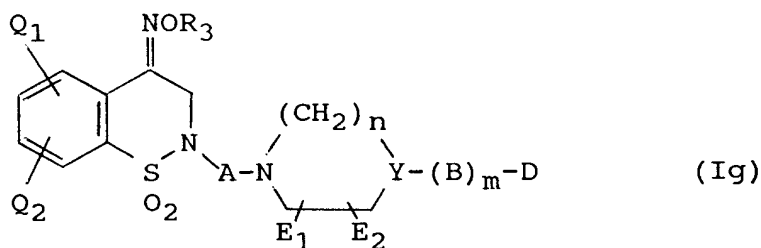


wherein A, B' , D, E_1 , E_2 , Q_1 , Q_2 , Y, m and n have the same meanings as defined above, which comprises subjecting a substituted benzothiazine derivative represented by the following formula (Id):



wherein A, B' , D, E_1 , E_2 , Q_1 , Q_2 , Y, m and n have the same meanings as defined above, to reduction.

17. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ig):



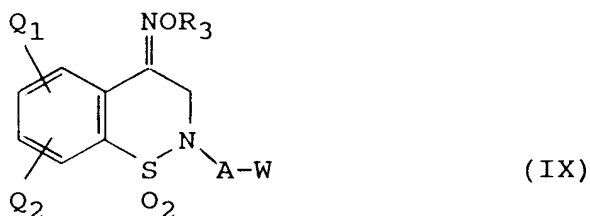
15 wherein A, B, D, E₁, E₂, Q₁, Q₂, R₃, Y, m and n have the same meanings as defined above, which comprises:
reacting a compound, which is represented by the following formula (VIII):



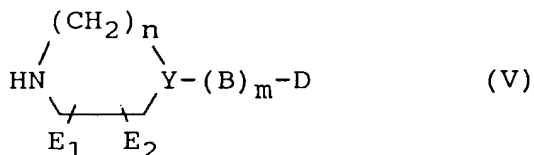
25 wherein A, Q₁, Q₂ and W have the same meanings as defined above, with a hydroxylamine represented by the following formula (VII):



35 wherein R₃ has the same meaning as defined above or with a derivative thereof to obtain a compound represented by the following formula (IX):

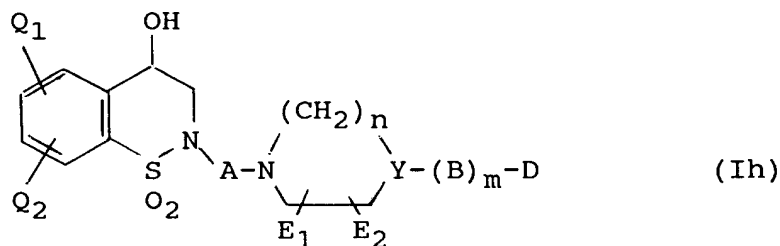


45 wherein A, Q₁, Q₂, R₃ and W have the same meanings as defined above; and then
reacting the resulting compound with a nitrogen-containing compound represented by the following formula (V):

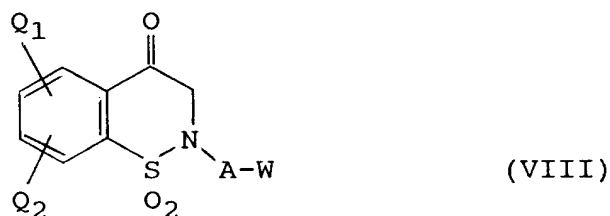


55 wherein B, D, E₁, E₂, Y, m and n have the same meanings as defined above.

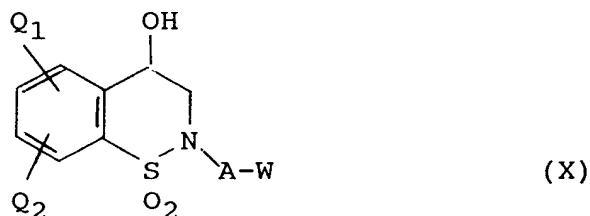
18. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ih):



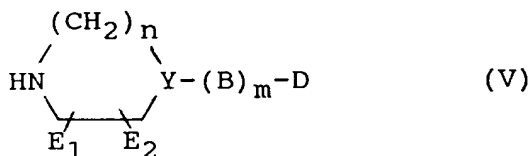
15 wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above, which comprises subjecting a compound, which is represented by the following formula (VIII):



25 wherein A, Q₁, Q₂ and W have the same meanings as defined above, to reduction to obtain a compound represented by the following formula (X):

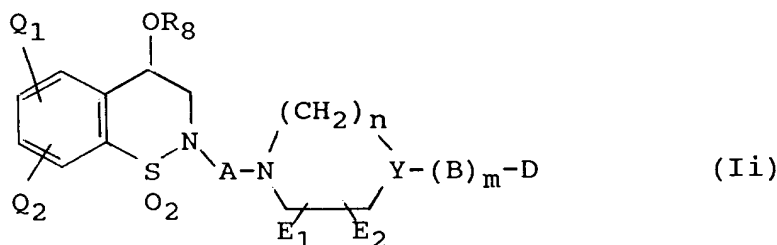


40 wherein A, Q₁, Q₂ and W have the same meanings as defined above, and then reacting the resulting compound with a nitrogen-containing compound represented by the following formula (V):



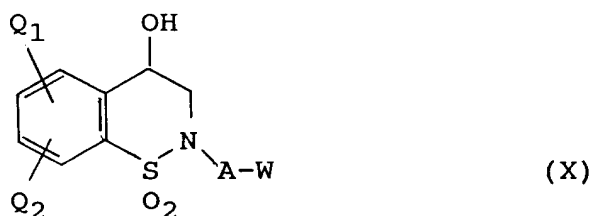
50 wherein B, D, E₁, E₂, Y, m and n have the same meanings as defined above.

55 19. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ii):



wherein R₈ represents a substituted or unsubstituted alkyl group or a substituted or unsubstituted aralkyl group, and A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above, which comprises:

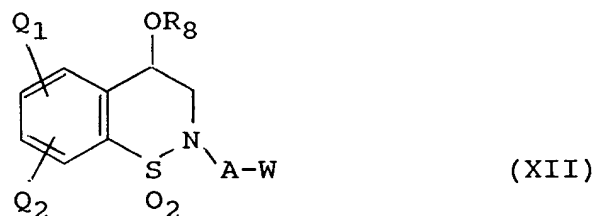
reacting a compound, which is represented by the following formula (X):



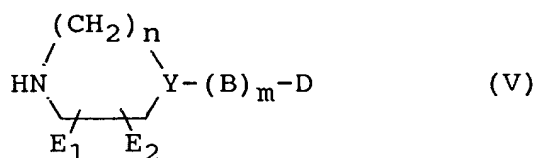
25 wherein A, Q₁, Q₂ and W have the same meanings as defined above, with a compound represented by the following formula (XI):



wherein W'' represents an eliminative substituent and R₈ has the same meaning as defined above, to obtain a compound represented by the following formula (XII):

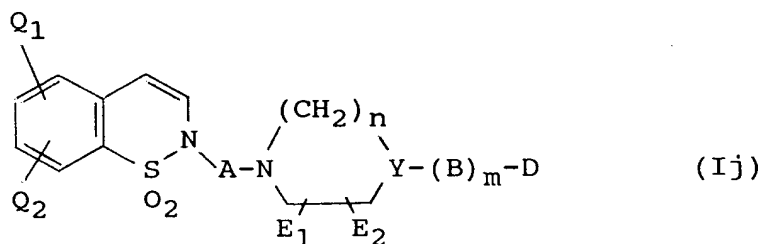


45 wherein A, Q₁, Q₂, R₈ and W have the same meanings as defined above and then, reacting the resulting compound with a nitrogen-containing compound represented by the following formula (V):

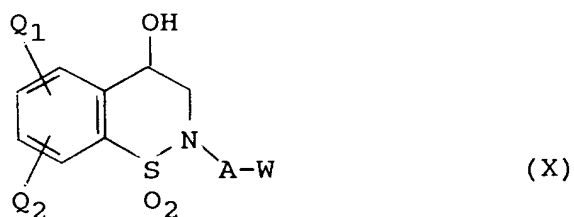


55 wherein B, D, E₁, E₂, Y, m and n have the same meanings as defined above.

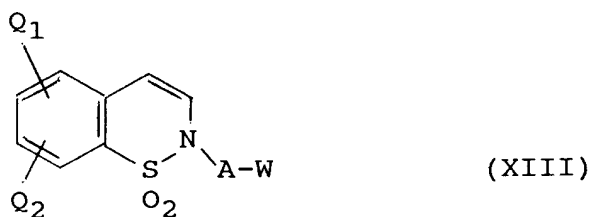
20. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ij):



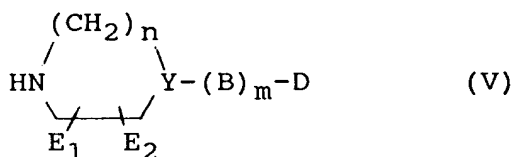
15 wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above, which comprises subjecting a compound, which is represented by the following formula (X):



25 wherein A, Q₁, Q₂ and W have the same meanings as defined above, to dehydration to obtain a compound represented by the following formula (XIII):

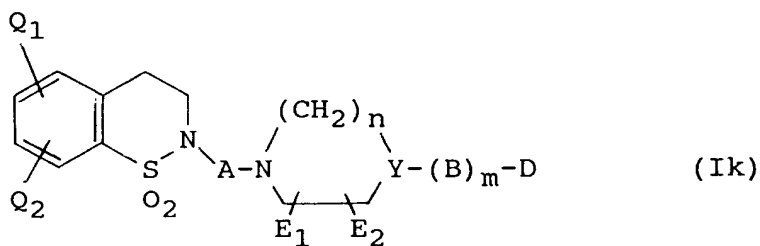


40 wherein A, Q₁, Q₂ and W have the same meanings as defined above, and then reacting the resulting compound with a nitrogen-containing compound represented by the following formula (V):

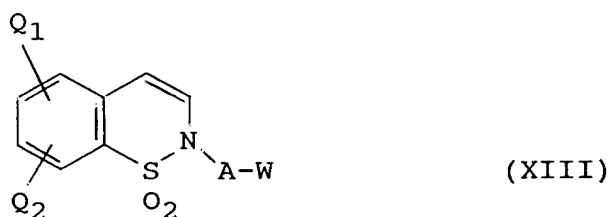


50 wherein B, D, E₁, E₂, Y, m and n have the same meanings as defined above.

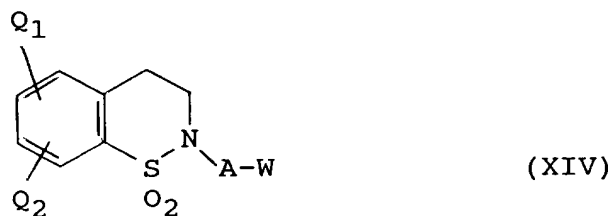
21. A process for the preparation of a substituted benzothiazine derivative represented by the following formula (Ik):



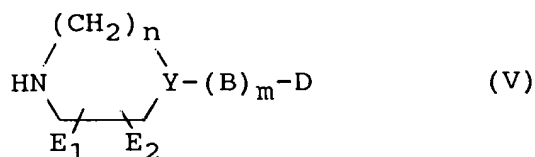
15 wherein A, B, D, E₁, E₂, Q₁, Q₂, Y, m and n have the same meanings as defined above, which comprises subjecting a compound, which is represented by the following formula (XIII):



25 wherein A, Q₁, Q₂ and W have the same meanings as defined above, to reduction to obtain a compound represented by the following formula (XIV):

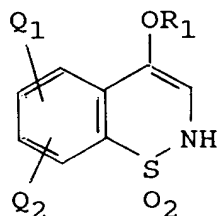


40 wherein A, Q₁, Q₂ and W have the same meanings as defined above, and then reacting the resulting compound with a nitrogen-containing compound represented by the following formula (V):



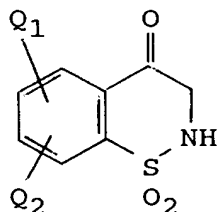
50 wherein B, D, E₁, E₂, Y, m and n have the same meanings as defined above.

22. A process for the preparation of a compound represented by the following formula (XVII):



(XVII)

wherein Q_1 , Q_2 and R_1 have the same meanings as defined above, which comprises reacting a compound, which is represented by the following formula (XV):



(XV)

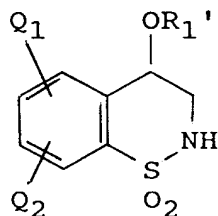
wherein Q_1 and Q_2 have the same meanings as defined above, with a compound represented by the following formula (XVI):



(XVI)

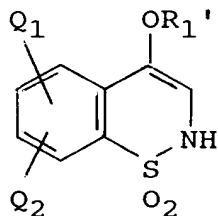
wherein R_1 has the same meaning as defined above.

23. A process for the preparation of a compound represented by the following formula (XIX):



(XIX)

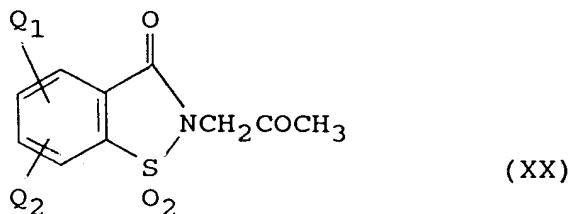
wherein Q_1 , Q_2 and R_1' have the same meanings as defined above, which comprises subjecting a compound, which is represented by the following formula (XVIII):



(XVIII)

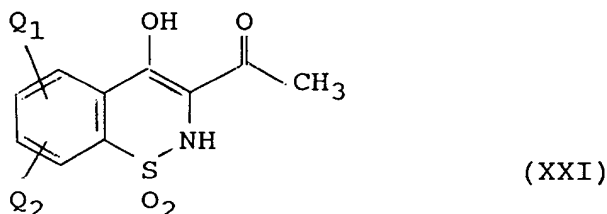
wherein Q_1 , Q_2 and R_1' have the same meanings as defined above, to reduction.

24. An intermediate suitable for use in the production of a pharmaceutical, said intermediate being represented by the following formula (XX):



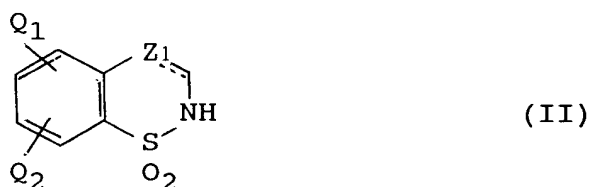
10 wherein Q₁ and Q₂ have the same meanings as defined above.

25. An intermediate suitable for use in the production of a pharmaceutical, said intermediate being represented by the following formula (XXI):



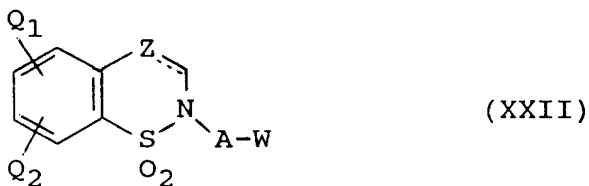
20 wherein Q₁ and Q₂ have the same meanings as defined above.

26. An intermediate suitable for use in the production of a pharmaceutical, said intermediate being represented by the following formula (II):



35 wherein Q₁, Q₂ and Z₁ have the same meanings as defined above.

- 40 27. An intermediate suitable for use in the production of a pharmaceutical, said intermediate being represented by the following formula (XXII):



50 wherein A, Q₁, Q₂, W and Z have the same meanings as defined above.

28. A pharmaceutical comprising as an effective ingredient a substituted benzothiazine derivative or a salt thereof according to any of claims 1 to 11.

- 55 29. Use of a substituted benzothiazine derivative according to any of claims 1 to 11 for the preparation of a pharmaceutical composition acting as serotonin-2-receptor antagonist.

30. Use of a substituted benzothiazine derivative according to any of claims 1 to 11 for the preparation of a pharmaceutical composition acting as a therapeutic for circulatory diseases.



European Patent
Office

EUROPEAN SEARCH REPORT

Application Number
EP 96 11 0050

| DOCUMENTS CONSIDERED TO BE RELEVANT | | | |
|--|--|---|--|
| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int.Cl.6) |
| X | US-A-3 284 450 (A. KRAAIJEVELD ET AL.) * the whole document, especially tables 1 and 2 (compounds 33, 34)* --- | 24,25 | C07D279/02 C07D275/06 C07D417/06 C07D513/10 A61K31/54 //(C07D513/10, 339:00, 279:00), (C07D513/10, 317:00,279:00) |
| Y | EP-A-0 433 149 (RHONE-POULENC SANTE) * the whole document * --- | 1-30 | |
| Y | WO-A-93 16073 (THE WELLCOME FOUNDATION LTD.) * claims * --- | 1-30 | |
| P,Y | EP-A-0 686 632 (SUNTORY LIMITED) * the whole document * ----- | 1-30 | |
| | | | TECHNICAL FIELDS SEARCHED (Int.Cl.6) |
| | | | C07D A61K |
| The present search report has been drawn up for all claims | | | |
| Place of search THE HAGUE | | Date of completion of the search 18 September 1996 | Examiner Chouly, J |
| <p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document</p> | | | |

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